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THE CHICAGO MEDICAL SCHOOL
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THE SPLEEN AS A FUNCTIONAL PROBLEM*

GEORGE J. SCHEFF, M.D., Ph.D.**

The physiology of the spleen has been an extremely controversial subject.[1, 2] This may have been due, in part, to the fact that we have been so poorly informed regarding the histological structure and normal function of this organ. It is difficult to reconcile that the spleen, on one hand, should be involved in so many diseases, and on the other hand, that its removal should be so well tolerated; indeed, splenectomy, under specified circumstances, can prove to be a life-saving procedure. Granted that we do not have all the answers to these and other questions, we still can ask ourselves: is it justified to single out the spleen as the organ of mystery in view of the fact that many other organs of the body also present unsolved problems? It would seem that we have learned a great deal about the spleen in recent years and within limits of space, this constitutes the material which will be discussed in the present paper.

Anatomy and Physiology

The spleen may be regarded as a vast lymph node which is composed of three essential tissue systems: 1) the vascular system, 2) the lymphoid network, and 3) the reticuloendothelial system. Each of these is endowed with characteristic functional properties which singly, or in combination, may become the cause of critical disturbances.

Let us investigate them individually:

It was known for quite some time that the spleen, principally through the network of sinusoids, is amenable to volume changes. In particular, the work of Barcroft and his school[3] has shown that the spleen can store blood (red blood cells and, in some mammals, significant volumes of plasma) and, by contracting in emergency conditions, can discharge its contents into the general circulation. In certain species, if the ejected blood volume is large enough, it may serve as an auto-transfusion. As a matter of fact, under circumstances of primitive existence, where hemorrhage can be combated only by natural forces, this mechanism may be a very important emergency function. That is probably the reason why carbon monoxide poisoning is better tolerated by a normal animal (guinea pig) than by a splenectomized one.[4] The carbon monoxide evidently does not combine for a period of two to three hours with the sequestered splenic blood and hence, enough free hemoglobin will remain available to combine with oxygen. In cyanide poisoning, which does not incapacitate the hemoglobin but affects the respiratory enzymes of tissue cells, normal and splenectomized animals succumb to the poison equally. In man, however, the splenic blood volume is small in proportion to the circulating blood volume so that the auto-transfusion effect becomes negligible.

There is, however, another phenomenon which, because of its intimate connection with the reservoir function of the spleen, deserves close consideration. It is based on the fact that the discoid red blood cells, by being retained in the spleen, undergo certain changes in form and become spherocytic. Although these form

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changes have been seen as early as 1854 (Gray), the rediscovery of this observation is credited to Fähraeus and Bergenhem (1921-1936).[5] Fähraeus studied the changes to which blood is subjected when kept *in vitro* at body temperature. He found that during incubation the high sedimentation rate gradually decreased; the discoidal shape of the red blood cells turned spherocytic; and the aggregation tendency, or so-called "rouleaux" formation, was diminished. Objectively, reduction of the boundary surface between erythrocytes and plasma was demonstrable, explaining the increment in the suspension stability of the blood (or conversely the decreased sedimentation rate) during stagnation. As the cause for this conversion of red blood cells, Bergenhem discovered the action of lysolecithin. Lysolecithin was believed to be produced in the serum from lecithin by the intervention of lecithinase. Unique as this thought may seem to be, it may be interesting to trace the idea which led to the discovery of this enzymatic reaction. From the literature prior to 1930, we see that ample observations were available as to how lipids, especially lecithin and cholesterol, affect the equilibrium of blood. It was also known that lysolecithin, a breakdown product of lecithin, and a component of snake venom, is a powerful hemolytic agent. It was only a step further to combine these observations and to formulate an appropriate hypothesis.

In order to transmit the *in vitro*-acting mechanism to a physiological process *in vivo*, Fähraeus and Bergenhem pointed out that an analogous process must exist in the spleen, since Barcroft's work had shown that the splenic blood can be shut off from the general circulation. This same viewpoint was adopted by Mellgren[6] and also Nordlander,[7] who also anticipated that under the conditions existing in the spleen a partial hemolysis takes place. Similarly, Ham and Castle[8] have shown that stasis *in vitro* as well as *in vivo* causes an increase in hemolysis. In fact, they furnished clear-cut experimental evidence that hemolysis is demonstrable outside the spleen in any part of the body (for instance in a tied-off leg of an animal), if the circulation of this part is temporarily excluded from the general circulation. From this, the obvious inference was drawn that splenic hemolysis is brought about through physiological erythrostasis. From the present outlook, it would seem that the splenic circulation would furnish the best clue for the understanding of the splenic function. So far, however, it is still obscure whether or not the spleen has a closed, open, or divided circulation.

Although the issue involved in this matter is primarily a morphological one, the functional aspects must also receive careful consideration. Björkman[9] combined the two viewpoints, and has shown, using Snook's staining method, that a widening of the so-called stomata in conjunction with a decreasing tightness of the sinus filter leads to sinus dilatation. Under such conditions plasma and corpuscular elements may escape from the sinuses into the pulp cords. From here, both plasma and corpuscles are forced back into the circulation via fenestrated collecting veins or the corpuscles are left behind in the pulp cords and returned into the sinuses. Concurrent with this process of separation and intimate contact with the reticuloendothelial elements, the red cells become deplasmatized and this, in turn, brings about their qualitative alterations and subsequent destruction. Pathological deviations are most likely due to a decrease in perviousness of the sinus filter with a longer retention of red cells in the pulp cords. Both of these mechanisms help to render the red cells more susceptible to hemolysis. This explanation is sound and is, thus far, the best which has been offered.

The role of the spleen in blood formation is another function which has been studied quite extensively. It seems well established that the spleen is actively erythropoietic during embryonic life. This, however, is of only short duration and usually ceases shortly before birth. What brings about the cessation of erythropoiesis is still obscure and presents a challenging problem. Later on in life, the spleen, as part of the lymphoid system, contributes some lymphocytes and perhaps a few monocytes to the circulat-

ing blood. The extent of this activity can not be very significant since after splenectomy, the reduction in the number of lymphocytes is negligible. In spite of this limited activity, the reappearance of ectopic blood forming foci would seem to indicate that the organ still remains a potential source of blood formation. In connection with hematopoiesis, an indirect effect also has to be considered. It has been often assumed that the spleen exercises some kind of remote control over the bone marrow (perhaps by way of the liver (Foa[10]). The hematopoietic crisis, consisting of leukocytosis, reticulocytosis, and rising platelet count, which follows the removal of the normal spleen, suggests an inhibitory action on the bone marrow. On the other hand, there is usually a concomitant anemia present which is somewhat contradictory to this view. The simultaneous appearance of young red corpuscles may be explained by assuming that the spleen influences not only the output but also the maturation of the erythrocytes. But this is by no means a settled question.

There seems to be little doubt that the spleen plays a prominent role in destroying the blood elements in one way or another. It is customary to refer to the spleen as the "grave yard" of the blood elements. However, the manner in which this destruction takes place in the normal individual is not fully understood. Hemolysis has already been mentioned as one form of excessive destruction of red cells during hemolytic crisis. But under normal conditions, lysis is not the usual manner in which red cells are destroyed. Two other alternatives have been considered: namely, phagocytosis and fragmentation. It is known that as part of the reticuloendothelial system, there are always some large fixed and wandering macrophages present in the spleen, which have an extreme avidity for removing foreign substances from the blood. Clasmatocytes also belong to the group of cells which physiologically engulf and metabolize worn out or damaged red blood cells, white blood cells, and platelets. Yet, phagocytosis alone does not explain the normal blood destruction satisfactorily. Rous[11] emphasized that phagocytosis is minimal in man and suggested fragmentation as the chief means of erythrocyte destruction. Be that as it may, there is ample evidence that the spleen participates in removing disintegrated red cells.

An interesting topic is the role of the spleen in the defense mechanism. The spleen, as we know, contains the largest aggregation of reticuloendothelial cells. Since these cells have, among many other features, the outstanding attribute of being the principal site of antibody formation, it was only natural to assume that it plays a very important part in the protection of the body. For many years this seemed to be well supported by experimental evidence. Splenectomy, or total blockade of the reticuloendothelial system, or both combined, were performed, and as a result, a decreased output in antibody production was generally established. There have been, however, many sources of error in these experiments. If, for instance, the blockade was incomplete, the antibody production was increased rather than decreased. It seems that the manner of administration and the amount of antigen injected is primarily responsible for the type of response obtained. Rowley[12] of Cannon's laboratory demonstrated that after intravenous injection, the spleen was the site of antibody formation, but only if small amounts of antigen were used. When large amounts of antigen were employed, the spleen ceased to be a determining factor. The great bulk of antibodies was produced elsewhere in the widely scattered areas of the reticuloendothelial system, and thus no distinct difference developed in the total circulating antibody titers of animals with or without spleens. When large or small amounts of antigen were injected intraperitoneally, or intraportally, removal of the spleen had no bearing on the antibody production. Evidently, the ultimate localization of the antigen in these instances must have been outside of the spleen.

In spite of this ambiguity in behavior with regard to antibody formation, the spleen seems to be essential in some way to the maintenance of natural resistance to certain bacterial and protozoan in-

fections such as tuberculosis, malaria, kala-azar, pyroplasmosis, and bartonellosis.

The relationship of the spleen to metabolism and its alleged hormonal effects has been the topic of many investigations. Since the spleen is a part of the reticuloendothelial system, there is little doubt that it is concerned with pigment and lipoid metabolism. It has been known for a long time that, under abnormal circumstances, huge quantities of lipoids may be deposited in the spleen, leading to splenomegaly. However, the interpretation of these observations has, of late, changed considerably. Whereas formerly it was believed that the lipoid deposits are displaced metabolites from some other part of the body, we believe now that the abnormal lipids, such as cerebrosides in Gaucher's disease, are due to a metabolic error affecting the intermediate stage of lipoid synthesis in the spleen. The proof for this was furnished by the fact that the sphingomyelin in the brain contains galactose as its sugar component, whereas splenic cerebroside is made up of glucose (Halliday et al.[13]). Splenic participation in protein metabolism has also been suspected. Whether this is due to the presence of lymphocytic aggregates in the spleen or to the activity of reticuloendothelial cell elements which are so abundant is still an open question. Additional study is necessary to clarify the respective roles of these cell types inasmuch as they may be related to the general immunological defense of the body.

Closely related to metabolism is the long-standing yet never proven contention that the spleen may possess endocrine potentialities. A great deal of circumstantial evidence but no valid proof had been furnished in this matter.[2] However, recent contributions to the subject have stimulated renewed interest with some encouraging results therefrom. We shall mention only a few of them, namely those of Erspamer, Moolten and Ungar. From the spleen, Erspamer[14] isolated a substance called enteramine which, in all probability, is a polyphenol derivative. It has a vasomotor effect apparently, which thereby influences the blood pressure. Moolten[15] described two substances extractable from the spleen. One of these is believed to elevate the platelet count, and the other to lower it. The latter substance might be identical with Troland and Lee's "thrombocytopen." Ungar[16], on the basis of his observations, assumed that two mutually antagonistic splenic principles, Splenin A and B, are released into the circulation. Whereas he found Splenin "A" to be physiologically active in blood, "B" was present normally in only very small amounts but became excessive under certain pathological conditions. It seemed that the fundamental action of the two splenins was related to the serum protease and antiprotease activity of the blood. The net result of the two was an inactivation of serum proteolysis which was accelerated by Splenin "A" and delayed by Splenin "B". "A" acted indirectly to protect the capillary endothelial bed and "B" damaged it. The indications are that both splenins are under the control of the hypophysis and the adrenal cortex, and, in this connection, may be tied up with the general adaptation syndrome. These findings have yet to be properly evaluated.

There is one more observation concerning splenic function which must still be corroborated. Cullumbine and Simpson[17] reported that toxic doses of the anti-thyroid compound, thiothymine (2-thio-5-methyl-uracil) are lethal to normal rabbits by causing pulmonary edema. The same drug remains ineffective in splenectomized animals. If, however, an aqueous acid extract of hog or beef spleen is injected concurrently with thiothymine, splenectomized animals also die of pulmonary edema. The splenic extracts alone are harmless. Similar observations were made by Tremonti[18] some fifteen years earlier, but they apparently remained unnoticed. Glass and the present author repeated these basic experiments but their findings have only partially borne out Cullumbine's observations. What reasons there may be for this discrepancy is difficult to explain. Differences in animal stock might be one cause, since Krumbhaar's review[1] mentions the fact that some rabbit strains have up to 75% accessory spleens and hence may have upset the conditions for reproducing

Cullumbine's results.

Pathological Involvements

Increased significance has been accaccorded to the spleen in various types of blood dyscrasias. It has been generally agreed upon that excessive splenic activity of some nature is capable of reducing the number of red blood cells, white blood cells, and blood platelets individually or in various combinations (hypersplenism). However, the exact mechanism of either of these conditions is still unsettled. The primary controversy centers about the issue as to whether the cytopenic state of different formed elements of the blood is brought about by excessive phagocytic activity of the reticuloendothelial elements of the spleen, or through elaboration of abnormal lytic substances by the same elements. Although it can not be denied that in splenic scrapings, stained supravitally, reticuloendothelial cells may occasionally elicit increased phagocytic activity, this is, in spite of statements to the contrary, by no means a constant sign. At present, it appears that the lytic concept is gaining prevalence. Nevertheless, it has become apparent that in the various hemolytic conditions, the lytic agents are not always the same. In congenital hemolytic icterus, the non-specific but strongly hemolytic lysolecithin is the agent most likely implicated. Indeed, it could be demonstrated that spleens from such patients show pronounced lecithinase activity (Scheff and Awny[19]). The failure of others to demonstrate lecithinase in the blood *in vivo* does not eliminate this agent from the picture, since the presence of inhibitory substances in the circulating blood precludes the possibility of their manifestation. On the other hand, if it is true that the blood in the spleen may be retained for various lengths of time, it is conceivable that in hypersplenism, the lecithinase will exert its activity partly because of the increased number of cells producing the enzyme, and also because during stagnation the inhibitory effect of plasma will be reduced to a minimum. In addition, more intimate contact of the retained blood cells with the freshly elaborated lysolecithin in the mesh-work of the pulp can be established. Such consideration will explain why this condition will gradually lead to red cell spherocytosis and sensitization of the erythrocytes to hemolysis. It explains why, following splenectomy, spherocytosis may still persist (because of continued formation of lysolecithin in other parts of the reticuloendothelial system), and why splenectomy itself is a life-saving operation (because at splenectomy, the principal site of red blood cell destruction is eliminated).

A closely similar idea has been invoked to explain the sequence of events in blackwater fever, where, apparently, increased lecithinase activity is also involved.[20]

In a number of other hemolytic conditions such as acquired hemolytic icterus, icterus neonatorum, etc., the existence of specific lytic agents has been demonstrated.[21] These agents, however, become hemolytic only under special conditions *in vitro*. Hence, their demonstration was, until recently, very difficult.[22] This is probably the main reason why their general acceptance has suffered such a long delay. *In vivo*, the pathologically altered spleen provides those conditions which bring about the lytic destruction of red blood cells.

A unique role is played by the spleen in Hemobartonella infection of rats.[23] In this infection, carrier rats will develop symptoms of severe anemia only after splenectomy. The most obvious explanation for this would seem to be that the agent remains latent as long as the spleen stays in the body. It becomes virulent only after the removal of the spleen, which deprives the animal of a hypothetical protective factor. The nature of this protective factor has, up to now, eluded discovery. Lauda[24] believed that it could be humoral in nature because, in his parabiosis experiments, neither the normal nor the splenectomized rat contracted the disease. Others, however, were unable to verify these observations. Perla and Marmorston-Gottesman[25] claimed to have extracted from fresh spleens a substance which protected splenectomized rats against Homobartonella infection. This claim has not yet

been confirmed either. We see, therefore, that although the mechanism of this infection has not been settled, the spleen nevertheless does play a major role in it.

These few examples illustrate the importance of the spleen in certain pathological conditions.

Splenectomy and its Occasional Failures

The striking successes in the early days of splenectomy initiated a mounting trend to remove spleens rather indiscriminately. This was primarily based on tne assumption that the spleen plays a non-essential role so far as normal health and longevity are concerned. It was also taken for granted that after removal of the spleen the symptoms of the former disease would not recur. Lately, however, an increasing number of hypersplenism cases have been reported which failed to respond to splenectomy, or which recurred after several years of remission. To avoid such unpleasant experiences, the indications for splenectomy should be carefully established. One must take into consideration the imbalance of the delicately poised equilibrium between the hematopoietic functions of the bone marrow and the inhibitory or hemolytic activities of the spleen. If the bone marrow is not functioning, the extirpation of the spleen, as a potential hematopoietic organ, will be detrimental. On the other hand, if accessory spleens are left behind, the recurrence of hemolytic disease is practically inevitable. Finally, there are cases of recurrences in which not even the autopsy can furnish any explanation. It is possible that in some of these unsuccessful splenectomies, the reticuloendothelial cells of the liver, lymph nodes, bone marrow, etc., assume the excessive destructive activities that usually are limited to the reticuloendothelial cells of the spleen. This is a very important point because it ties the spleen to other parts of the reticuloendothelial system, all of which comprise a functional entity.

Conclusion

An attempt has been made to show that the enigma surrounding the spleen has been clarified to a large extent in recent years. A knowledge of its normal functional behavior is essential to the proper understanding of this organ. Many of the pathologic aberrations can be explained by assuming hyperactivity on the part of the spleen. There are still a few other splenic conditions wherein the mechanism is obscure. Still, it would seem that with the intense work going on in this field, the solution of the entire problem is not too far away.

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SEROLOGIC ASPECTS OF THE Rh FACTOR*

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Literature on the Rh factor has been growing rapidly so that one can hardly open a number of a current medical journal without finding an article on or a reference to this subject. In spite of that there seems to be considerable confusion regarding the Rh factor. Frequently, it takes the form of something akin to revulsion when the subject is mentioned. I believe that this discrepancy between the available information and the lack of true understanding is due to two factors. One of them is that many writers on the subject deem it necessary to write about everything that is known about the Rh factor, including some aspects of it which are of interest only to the specialist. The other reason is that the Rh factor is discussed as something entirely separate from the other blood factors. Thus, there is lacking the understanding of certain aspects which would contribute to clarity. I should thus like first to present a few fundamental principles.

The Rh factor is one of several factors present in human blood. The term factor means an antigen in the red blood cells capable of producing specific antibodies and of reacting with them in the test tube. The specific antibody agglutinates red blood cells and/or hemolyzes them.

There are three systems of blood factors in human red cells:

1. The system of the ABO factors, the basis of the division of human blood into the four main classical blood groups. There are natural antibodies against the factors A and B in human blood. Therefore, they were the ones first to be noticed, because we can recognize the factors only through the antibodies.

2. The system of blood factors M and N. There are no natural antibodies against these factors and none are produced in man in the course of transfusions. A few isolated instances of isoagglutinins against M and N have been reported. Their genesis is unknown. These two factors have no clinical significance. Their application is limited to legal medicine where they are used, together with the other blood factors, for identification of blood, especially for exclusion of parentage.

3. The system of the Rh factors. It is important to know that the division into Rh-positive and Rh-negative does not give a complete picture of the Rh system. Actually, there are several types of Rh factors. More about them later.

As stated before, all blood factors are antigens. A substance which does not have most of the properties of an antigen, but has only the property of absorbing or reacting with the antibody without being able to produce it, is a half-antigen, or a hapten.

In the ABO system there are antibodies or isoagglutinins against factors A and B present naturally. There are no natural isoagglutinins against M and N and none are produced when blood of one type is injected into a person who does not have it. In the Rh system there are no natural agglutinins against Rh, but following injection of blood containing the Rh factor into a person who does not contain it, antibodies develop. There are as many types of antibodies as there are different Rh types. With the help of the different Rh antibodies, several types of the Rh factor have been discovered. The most frequent and the most important of them is one which is known as Rh_o, or D (according to the British nomenclature). This is present by itself in about 2½ percent of the white population and in a much larger number among negroes. However, in combination with the other two factors to be discussed later, this Rh_o or D factor is present in 85 percent of the population. The next type of Rh is known as rh′ or C. By itself it is present in about 1½ percent, but together with the Rh_o it is present in about 25 percent.

In addition, there are types known as hr′ or c, hr″ or e and Hr_o or d. The

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symbols, D, d, C, c and E, e are used in the British nomenclature of Race and Fisher. Of these various types, the most important is Rh_o or D, not only because it is the most common, but because it is the most potent of the Rh antigens. From the clinical point of view, the Rh_o (D) and rh or the Rh-negative, are the two most important types. These Rh factors, just as the MN and ABO, are inherited according to the Mendelian laws of heredity.

An Rh-negative individual receiving transfusions of Rh-positive blood, or an Rh-negative woman pregnant with an Rh-positive fetus, becomes readily sensitized and this sensitization is, as a rule, a lifelong condition. It is claimed that about 50 percent of Rh-negative individuals who receive an Rh-positive blood transfusion become sensitized. Sensitization during pregnancy is apparently less readily acquired because it takes more than one pregnancy, as a rule, for it to develop.

The practical application of our knowledge of the Rh factor has influenced profoundly the practice of blood transfusions. If donors are carefully selected and only homologous Rh blood administered, then most of the unexpected transfusion reactions that used to be so troublesome in the past can be eliminated. It is desirable that only homologous Rh blood be given: i.e., Rh-negative blood to Rh_o-negative recipients. In the case of women recipients, the urgency of using only homologous Rh blood is still greater, because, in addition to the handicap of developing sensitivity and being endangered in case of a future transfusion by becoming sensitized in this way, their first born children may have fetal erythroblastosis, otherwise a rare occurrence. Women sensitized by transfusions may never be able to give birth to a healthy child.

It is now generally agreed that over 95 percent of cases of fetal erythroblastosis are due to Rh incompatibility between mother and child, usually in such a way that the mother is Rh-negative and the child Rh-positive.

The development of Rh antibodies in the mother as a result of the entrance of Rh-positive blood or of its components through the placenta from the fetus into the circulation of the mother, and the passage of such antibodies back from the mother through the placenta into the fetus, with consequent damage to the fetal blood, anoxia, damage to the liver, to the brain, etc., is the recognized pathogenesis of fetal erythroblastosis. All manifestations and pathologic changes can easily be explained in this way.

The serologic set-up of Rh incompatibility favoring erythroblastosis exists in approximately 13 percent of marriages and in about 10 percent of all births, because it is in this 13 percent of marriages that the husband is Rh-positive and the wife is Rh-negative, and in 10 percent of births that the mother is Rh-negative and the child Rh-positive. In spite of that, the incidence of the disease is actually considerably less, about once in from 200 to 300 deliveries.

The explanation is that it takes, as a rule, more than one pregnancy for sufficient sensitization to develop. The antigen varies in its antibody stimulating capacity. The antibody producing capacity of women is a biologic phenomenon which differs from person to person. Finally, the factor of permeability of the placenta for the antigen from the fetus to the mother and for the antibodies in the opposite direction is apparently a variable quality. All this explains the discrepancy between the possible incidence of erythroblastosis and its actual occurrence.

Fetal erythroblastosis due to Rh incompatibility is also possible in children of Rh-positive mothers and is caused by the difference in the types of the Rh factor.

The Diagnosis of Fetal Erythroblastosis.

The diagnosis can be made from clinical findings, supported by hematologic data. The pathologist can make the diagnosis from autopsy findings. There are also serologic findings based on the study of the Rh factor, which are at least as important as the clinical and anatomic and sometimes even more decisive. Here, I shall take up only the serologic diagnosis, which can be divided into prenatal and postnatal, depending upon the time when one is called upon to make the

diagnosis.

The first condition that has to be fulfilled is finding evidence of serologic difference, i.e., the husband has to have a different Rh type than the wife. Most frequently, the husband is Rh_0 (D)-positive and the wife Rh-negative. Other forms of type difference occur occasionally. However, one must not draw too far-going conclusions from finding this serologic difference in Rh type. Serologic incompatibility is present when, in addition to Rh type difference, there is evidence of Rh sensitization of the mother to the husband's blood antigen. One has to be on guard against the possibility that the sensitization and Rh antibodies are the result of a previous pregnancy, or of a previous transfusion of blood, and must not necessarily be the result of the current pregnancy. Sometimes one may observe the phenomenon of so-called anamnestic reaction, antibodies being present in low titers or sometimes even elevated titers but being the result of previous pregnancy or transfusion. Such antibodies are called carry-over antibodies.

There was a time when we used to find Rh antibodies in mothers of babies with erythroblastosis only in a relatively small percentage of cases. Now, with the improved methods of determination, we find them in almost 100 percent of cases. These improved methods include the use of diluents containing a high concentration of protein, such as 30 percent albumin, the use of serums produced in rabbits against human protein and capable of detecting a very fine layer of Rh antibodies deposited on the surface of red blood cells, the so-called Coombs' test, and finally, the most recent procedure which employs trypsin and other enzymatic substances which act on the surface of red blood cells and make them susceptible to the action of Rh antibodies. This procedure makes it possible to detect traces of antibodies that could not be detected before. Therefore, the absence of Rh antibodies is so rare a phenomenon that it may almost be used to exclude the diagnosis of fetal erythroblastosis. Another important fact to remember is that, whereas the titer of antibodies may be so low as to be hardly detectable at the end of pregnancy and even immediately after childbirth, the examination about 10 to 12 days after delivery may detect a substantial titer. The study of these serologic factors, i.e., Rh type differences and evidence of Rh sensitization, may help considerably, especially in cases where the differential diagnosis of fetal erythroblastosis has to be considered.

The postnatal diagnosis of fetal erythroblastosis is made on the basis of clinical findings and, in the case of an autopsy, of postmortem findings. There are certain important diagnostic laboratory procedures which I shall not discuss here, but the serologic examination of blood for antibodies is very important.

Occasional cases of severe anemia in children several months old, of late kernicterus, etc., may also require serologic study as a help in the diagnosis. These are cases of late fetal erythroblastosis in which the disease may have been absent in the neonatal period or it may have been very mild and was overlooked.

Another form of the disease in which serologic studies may be of extreme importance is so-called latent erythroblastosis, occurring in children born with no signs of the disease, but in whom the disease becomes manifest, sometimes in a very severe form, on the second or third day of life. Early therapy immediately after birth may be decisive in saving such infants. In such cases, several laboratory tests may be of great help in influencing early suitable therapy. These laboratory tests include a blood count and hemoglobin done on the cord blood. It has been shown that blood counts and hemoglobins done on peripheral blood of newborn babies are notoriously unreliable, partly because tying the umbilical cord late may give the baby an amount of blood equivalent to a blood transfusion, and vice versa, tying it early may deprive the baby of a similar amount. Hemoglobin of about 14 Gms. and a red count of about 4½ million are to be considered as indicating anemia. In view of the fact that only Rh-positive children can have fetal erythroblastosis due to Rh incompatibility, this finding at birth favors the possibility of the dis-

ease. Finally, a Coombs' test done with the already mentioned anti-human rabbit serum, if positive, favors the diagnosis of latent fetal erythroblastosis. It proves that Rh antibodies from the mother have entered the circulation of the baby and have been deposited on the baby's Rh-positive blood.

The Prognostic Value of Serologic Tests

The serologic examination of the mother's blood for antibodies is of paramount importance for the prognosis. It is the question of prognosis which so frequently confronts the physician. Several factors should be kept in mind. Much depends upon the parity of the patient. A woman who is found to be Rh-negative, whose husband is Rh-positive, and who is in her first pregnancy has an excellent chance of having a perfectly normal first child, because first-born children are very rarely affected by the disease. However, certain circumstances have a definitely aggravating significance. They include a history of abortion. Abortions have a similar though less pronounced sensitizing influence as have pregnancies. Also included, of course, are stillbirths, which have even a more serious prognostic significance. Transfusions, unless it is known that they were given with homologous Rh blood, have such a similar aggravating significance. It was shown that a great many cases of erythroblastosis in first-born children could be traced to sensitizing influence of a transfusion of non-homologous Rh blood. Twins seem to have a greater tendency to produce sensitization. It is possible that the double dose of the antigen may be a factor.

Another prognostically important consideration is the Rh_0 homo- or heterozygosity of the father. If he is homozygous Rh_0-positive, i.e., he inherited the Rh_0 (D) factor from both parents, then the prognosis is much worse than otherwise, because an Rh_0 heterozygous father has the possibility of giving issue to an Rh-negative child, while all children of Rh_0 homozygous fathers have to be Rh_0-positive and hence subject to the disease.

Studies of Rh antibodies during the pregnancy may be of prognostic significance. Here it must be kept in mind that there are several types of antibodies varying considerably in their prognostic significance. There is, for instance, the type of Rh antibodies which react when salt solution is used as diluent for the serum as well as a menstruum for the suspension of red blood cells used in the test. This is known as the so-called saline antibody. Another type of antibody cannot be detected with this set-up employing saline, but one has to use either human serum or a concentrated solution of albumin, human or bovine. The latter is preferable and is available in 30 percent concentration. The prognosis in cases when so-called serum albumin or conglutinating antibody is present is much more serious than when only saline antibodies are present. The third variety is one where the antibodies are present but they do not agglutinate red blood cells and can be detected only by means of an indicator which shows that the red blood cells have been coated with antibody and that this coating antibody interferes with or blocks the action of subsequently added antibodies. This is the so-called blocking antibody, which has the most serious significance of all the three varieties, because a majority of women, having developed such blocking antibodies during and as a result of the pregnancy, have stillborn babies, as a rule due to fetal hydrops. It is, therefore, important to do tests for antibodies and to do them for all these three varieties.

It is desirable to do the tests repeatedly during the pregnancy, the first time before the end of the first trimester, because antibodies found that early in pregnancy are, as a rule, due to a previous pregnancy. It is obvious that interpretation of antibodies is dependent on the knowledge that they have or have not developed as a result of the current pregnancy. One may, for example, be disturbed by antibodies found in the latter part of pregnancy and then be surprised by the birth of a perfectly normal Rh-negative child. An examination done during the first trimester of pregnancy could have disclosed the presence of antibodies which, at that time, cannot be due to the current pregnancy.

There are different opinions regarding

the advisability of doing these tests during the pregnancy and regarding the frequency with which they should be done. I believe, that in addition to the tests done during the first trimester of pregnancy, at least three more tests should be done: one sometime during the fifth month of pregnancy, another during the seventh month and the third one preferably immediately before delivery. In this way one may be able to get an idea about the trend of the antibody development. In our own laboratory we recommend doing these tests at monthly intervals and during the last few weeks even more frequently. We found, that when antibodies are absent during the pregnancy and appear for the first time four weeks or less before delivery, we can be very hopeful that the child will not be affected at all or only very mildly. The finding of antibodies for the first time about two months or less before term is also a good prognostic implication. On the other hand, the finding of antibodies during the fourth or fifth months of pregnancy has a serious implication.

Also significant is the titer of the antibodies. Here, again, one can draw no conclusions from a single examination. A consistently high titer, and especially a rising titer, make the prognosis serious. The value of such repeated tests is twofold: they permit making a cautious prognosis; they warn of danger and permit making suitable arrangements prior to the delivery.

Serologic Aspects of Treatment

It is generally agreed that Rh-negative blood should be used in spite of the fact that the infants are themselves Rh-positive. The reason for it is that there are Rh antibodies in the circulation or attached to the reticuloendothelial tissues of the infant which react or may react with the injected Rh-positive blood, thus contributing to the continuation of the disease and to its possible aggravation. It is recommended to give 10 cc. per pound of body weight.

Recently, there is a tendency to give resuspended Rh-negative blood, that is blood cells without the plasma. The removal of the plasma is justified by the assumption that adult plasma contains a factor necessary for the agglutination of red cells and its addition is supposed to favor such agglutination. According to some, clinical experience seems to support the use of such resuspended blood.

Replacement or exchange transfusion cannot be done with resuspended cells, because one cannot deprive the infant of plasma. However, it has been recently recommended to use a modified replacement transfusion by exchanging 120 cc. of packed red blood cells without the plasma with 120 cc. of the infant's whole blood. Good results are claimed by those who advocate this procedure.

Indication for blood transfusions is the presence of clinical fetal erythroblastosis. In the case of latent fetal erythroblastosis the findings as outlined previously of anemia in cord blood, of a positive Rh factor in the cord blood of the newborn, and of a positive Coombs' test, together with a history of erythroblastosis in a previously born infant are, according to some, an indication for a replacement transfusion, even in the absence of clinical manifestations of the disease. When the past obstetrical history is negative for erythroblastosis the presence of the other findings justifies, according to some, the administration of a regular small transfusion.

The most important contribution to the prevention of fetal erythroblastosis is the recognition of the relation between incompatible Rh transfusion and erythroblastosis in the first-born baby, suggesting the absolute indication for Rh homologous blood in transfusions to women regardless of age. It has also been suggested that occasionally, intramuscular injections of blood given to young infants or children may mean sensitization and trouble in the future. The objections that can be raised against it, in view of the small amount of blood injected intramuscularly, is countered by the fact that some individuals are apparently very prone to sensitization and that in such cases the quantity of the antigen may not be extremely important. Attempts at prevention of the disease by injection of other antigens, for example, pertussis vaccine, on the basis that when several antigens are administered at the same time, the

weaker antigens, and Rh is one of them, have less opportunity to sensitize, do not seem to have been borne out by actual observation. It has also been suggested that spacing of pregnancies at greater intervals may be a beneficial factor. This is more an academic observation than one based on fact, because the sensitization is usually so powerful that the possible intervals would hardly be of practical significance.

The recent publicity regarding the beneficial effect of hapten seems to have been based on insufficient facts. There is no reason to believe that an Rh hapten has been produced and that the administration of the substance called Rh hapten would lead to the desired desensitization. It is probably unwarranted, by what is known today, to recommend its use.

There are occasional cases of what clinically looks like erythroblastosis, not due to any detectable or even possible Rh incompatibility, in the presence of AB incompatibility or a so-called heterospecific pregnancy. There is much division of opinion regarding the possibility of fetal erythroblastosis due to AB incompatibility. Some of us believe that it is possible, and cases have been described with very high titers of anti-A or anti-B agglutinins to corroborate it. It seems that there are cases of the disease which are best explained in this way. The difficulty is that we have no reliable means of differentiating between immune anti-A and anti-B agglutinins and so-called natural agglutinins. Our own experience in close to 40 cases has been that this disease caused by AB incompatibility is, as a rule, much milder than the one caused by the Rh factor incompatibility. However, we did observe several cases with fatal outcome. Whenever a possibility of fetal erythroblastosis caused by AB incompatibility is being considered, it should be kept in mind that the infant should be given O blood transfusions, preferably resuspended O cells. The infant should not be given compatible A or B blood for the same reason that Rh-positive babies with erythroblastosis are not given Rh-positive but Rh-negative blood. It has also been recommended, and reasonably so, to give these babies so-called blood group specific substances which are concentrates of A and B factors intravenously in order to neutralize the antibodies.

In summary, there are five important points to be remembered:

1. Homologous Rh blood should be used for transfusions of women regardless of age.

2. The presence of fetal erythroblastosis in a newborn baby is an indication for the transfusion of Rh-negative blood in one of several ways that have been described. According to some even latent fetal erythroblastosis with a history of the disease in previous babies is an indication for transfusion.

3. Much information of diagnostic and prognostic significance may be obtained by examination of the blood during pregnancy. In such a case, all three varieties of antibodies should be examined, and the test should be done repeatedly, the first time during the first trimester.

4. The examination of the husband's blood for homo- and heterozygosity may be valuable prognostically.

5. If erythroblastosis caused by AB factors is suspected, the infant should be given blood of group O and not homologous blood.

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SOME PUBLIC HEALTH ASPECTS OF BACTERIAL WARFARE

With Special Reference to Urban Areas[1]

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The most serious aspects of communicable disease problems of "all-out" warfare are not those involved with the use of atom-bombs, but are a series of rather diverse problems grouped under the heading "Bacterial Warfare," commonly termed "B.W."

Bacterial warfare can be defined as "the planned and calculated use of microorganisms and/or their products for the physical (and psychological) debilitation of enemy troops and civilian populations, or their animals and livestock, and of their crops." Thus, not only are bacteria included, but also other types of disease organisms and vectors, *e.g.* viruses, rickettsiae, protozoa, insects, fungi, etc., and their products.

As Rosebury and Kabat (1947) point out, infective agents of communicable diseases have a property not possessed by poison gases—and hence have a great advantage over chemical warfare—that of *epidemicity*, or capacity to spread from one infected man (or animal, or plant) to others, and thus continuing to spread over a large area, and act for prolonged periods.

There have, to date, been only a few well-authenticated cases of actual use of bacterial or microbiological warfare: in Nov. 1941 the Japanese deliberately seeded the town of Changteh in North Central China with rat fleas infested with *Pasteurella pestis*, the causative agent of bubonic plague, and within a week an epidemic of plague erupted there; the deliberate destruction of the drainage canals and the subsequent reflooding of the Pontine Marshes in Central Italy by the retreating Germans in 1944, thereby causing subsequent epidemics of malaria in an area previously freed of the disease; the nightfall and early dawn bombings and strafing by American fliers of Japanese bivouac areas in New Guinea and other Southwest Pacific Islands from 1943-1945 so that the troops were forced to leave the protection of their bednets or mosquito bars and dive for cover in outside foxholes where they were immediately set upon by anopheline mosquitoes and suffered increased malaria debilitation; the use of hoof-and-mouth disease virus by the Germans among the cattle of the Sudetenland Czechoslovakians before its annexation by Hitler; the reputed seeding of water supplies by the Italians in Ethiopia with typhoid organisms; and the destruction by American fliers of Japanese vegetable gardens by spraying them with herbicidal oils and chemicals in 1944-1945 in the Southwest Pacific, about completes the roster.[2]

It should be pointed out that the use of microbiological agents in bacterial warfare is the "great equalizer"—making small, relatively industrially undeveloped countries the equal of the United States as a menace in warfare. Perhaps even a greater danger is that they can be used as a desperate resort with some justification. No great body of highly trained technicians is required; no large industrial plants; no great financial or gold stockpile; no large populations for the production and intelligent dissemination of the causative organisms. A medium-sized distillery would be to biological warfare what the Hanford plutonium pile is to atomic warfare. Research on B.W. can be carried out in any public-health laboratory under the camouflage of legitimate activities.

Although there are international conventions against the use of bacterial and chemical warfare, it is the military opin-

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2. Natural pestilence has decided more campaigns than generals. As Pier (1946) points out, "On the plains of Thessaly, epidemics killed nearly two-fifths of Xerxes' 800,000 troops. Plague and typhus slaughtered the Crusaders at Antioch and Jerusalem. Typhus, not Ferdinand and Isabella, liberated Granada from the Moors. Typhus and dysentery decimated Napoleon's Grand Army in Russia." Until World War II, more soldiers died from diseases than bullets. In many areas American casualty rates from malaria and dengue fever were ten times those of casualties due to enemy action.

ion that any weapon is useful if it accomplishes a military purpose, *i.e.* the destruction or immobilization of men, without excessive risk to the user.

The danger is real and is great. The cloak of secrecy which has surrounded the discussion of this topic while quieting the spectre and calming the populace has not lessened the danger nor removed the cause one whit.

The principles of bacteriological warfare are not well known, but are exceedingly complex. Their foundation rests on modern bacteriology and pathology; the sciences of epidemiology, demography, chemical warfare, meteorology, physical chemistry, pedology, water and sewage sanitation, entomology, ecology, sociology, industrial engineering, and tactics of warfare. In short, an analysis of the whole complex of modern society and warfare supplies the data on the recipients; the fields of pathology and the epidemiology of rises and falls in epidemics supplies the data on the maintenance and effects of the use of these agents. The physical chemistry of aerosol and smoke production and spread, the meteorology of wind currents, inversion conditions and flight patterns govern the distribution and spread of the respiratory and air-borne agents. The sciences of soil use and drainage, water supplies, food and livestock production and utilization govern the distribution and spread of food and water-borne infections. The sociological intercourses of man himself govern the distribution and spread of contact infections and the maintenance and spread of some of the air and food-borne infections. The sciences of mammalogy and entomology and their handmaiden, ecology, govern the distribution, maintenance and spread of vector-borne infections, — all various aspects of the maintenance problem. Finally, the whole field of the bacteriology of communicable and infectious disease microorganisms supplies our raw material, the actual agents which are to be used.

We can not cover any of these subjects in great detail and therefore will skim over some of the highlights, restricting ourselves to the use of the B.W. agents against civilian urban populations, rather than their use against troops dispersed in the field.

Principles of Bacterial Warfare:

An exhaustive analysis of the problem of B.W., made by Rosebury and Kabat in 1942, showed that effective dissemination of disease agents in warfare is a distinct possibility. The potentially effective agents for warfare have to meet certain criteria, however. Among the most important of these are:

1. *infectivity*—can the organisms attack humans? are the hosts susceptible, resistant, or immune?
2. *casualty effectiveness* — degree of immobilization produced by the agent? incubation period? severity and duration of course and convalescence? case mortality?
3. *availability*—cultivability on media or tissue or egg culture? maintenance in vectors, animals, or other means? mass production methods? stability of virulence after production?
4. *resistance of the organism*—methods for maintenance of virulence for long periods? means of disinfection?
5. *means of transmission*—known natural routes of transmission, common and alternate? additional means of transmission?
6. *epidemicity* — capacity for spread from man to man or from animal to animal?
7. *specific immunization* — effectiveness of and availability of means for immunization? can whole population be immunized against the threat?
8. *effect of therapy*—effectiveness and availability of specific therapy and chemotherapy?
9. *detection*—ease or difficulty and the means of detection and identification of the agent for bacteriological diagnosis of the disease?
10. *possible retroactivity*[3] — likelihood and probable degree of danger in use to attacking force, and their

3. Many of the organisms are dangerous to handle, and thus constitute a hazard to the producer and user as well as to the victim.

own means of protection or control?

As each organism or disease is analyzed under the above headings in the light of maximum damage to the enemy with minimal danger to oneself, it is possible to pick out the most likely agents which might be used. We will discuss some of the most likely of these agents, their characteristics, and the dangers inherent in them.

Many communicable disease are not suitable for a variety of reasons, *e.g.* in cholera and typhoid, sanitary precautions can be instituted easily, and the population immunized; in diphtheria, there is a low attack rate in adults; in actinomycosis, the organisms are endogenous; in leprosy, tuberculosis, and rabies, the incubation period is too long and there is a low attack rate; in the various venereal diseases, dissemination is impractical; in polomyelitis, the virus is already indiginous in the population, the attack rate is low, and the virus can not be cultivated in large amounts; and in many of the insect-borne diseases, *e.g.* the leishmaniases such as Kala-azar, the trypanosomiases such as African sleeping sickness, relapsing fevers, pappataci fever, spotted fevers, etc., the development of the microorganism is biological and the ecological requirements of the vectors are too exacting. They probably will not establish themselves here. In some, the causative organisms are either not known or can not be cultivated except with difficulty, and hence are unavailable; in others, such as staphyloccal and streptococcal infections, there is a low infectivity rate; in still others, such as rat-bite fever, the disease is too difficult to transmit; and in still others, such as tetanus and smallpox, the populace can be immunized.

Many of potentionally dangerous diseases are not suitable for B.W. when used alone, but are suitable when used in combinations, such as pooled staphylococcus and streptococcus, and pneumococcus with staphylooccus. They are then more highly pathogenic and have a higher infectivity rate.

The greatest danger in B.W. at the present time is two-fold:

1. that the enemy, as we ourselves already have, by genetic selection, rapid passage, passage through resistant hosts, and physical mutation will be able to produce genetically different strains of well-known organisms which are highly pathogenic to man or animals and attack a greater proportion of individuals, —so much so that the disease they produce is essentially a new disease. They may also produce strains completely resistant to our standard therapeutic agents, all the known usable antibiotics and sulfonamides,[4] and which are capable of breaking down the immunities produced by previous vaccinations.
2. that the enemy, as we ourselves already have, will isolate entirely new types of pathogenic organisms, microbial products, etc., which heretofore man has not been in contact with and against which he has not built up any immune defenses.

These conditions, still under the "SECRET" category, will radically modify our concept of the potentialities of B.W. For example, Rosebury and Kabat (1947), in their analysis of the problem, listed Friedlander pneumonia, caused by Friedlander's bacillus, as of no importance in B.W. because of its low infectivity. However, it may now be considered one of the greatest dangers—its previously high pathogenicity has been multiplied, its infectivity greatly increased, and it is highly resistant to most antibiotics.

Types of Transmittable Diseases:

The transmission of communicable diseases falls into five main types:— a) the food and water-borne group; b) the contact group; c) the air-borne group; d) the vector-borne group; and e) the endogenous group.

A. The Food and Water-borne Group.

These diseases are divided into 1) the ingestive—in which the infective agent enters the body selectively through the alimentary tract; and 2) the water-con-

4. A fairly simple procedure, brought about by growing the organisms for a prolonged period of time in media with gradually increasing concentrations of the therapeutant or combinations of the therapeutants.

tact diseases—in which the organisms enter the body through the skin.

In the ingestive diseases we find:

The water-borne epidemic diseases like cholera, typhoid, paratyphoid, etc., which result from pollution of water supplies by fecal contamination from a case or a carrier of these diseases. When large numbers of persons drink such polluted water, as may occur in a city using a common water supply without sanitary precautions, explosive outbreaks occur. There have been many such large epidemics of such diseases, not all of them limited to the Far East. Hamburg, Germany, had such an outbreak of cholera in 1892 with 17,000 cases and 9,000 deaths in a 6-week period. Cairo, Egypt, in 1947 suffered another with 21,000 cases and 10,250 deaths in an 8-week period. This last was brought under control by widespread vaccination.

Since these diseases may be prevented easily by sanitary means: boiling of water, chlorination, filtration, etc., and effective vaccines are available, they are not considered important agents in urban B.W.

The food-borne infections, e.g. staphylococcal food poisoning, salmonella enteritis, bacillary and amebic dysentery, and botulism, which cause severe gastroenteritis in man. They cause severe acute incapacitations, but low mortalities. The agents can all be water-borne as well as food-borne, and this former is the more important for B.W. since they can reach larger numbers of individuals. Bacillary dysentery and botulism are considered the most important of these from a B.W. standpoint. They can be introduced by saboteurs into the food or water supply, or canning industry. Botulinus can be introduced either as the organism, the resistant spore, or the toxin itself.

1. *Botulism.* Botulinus toxin is the most potent poison known. It is 10,000 times as toxic as potassium cyanide; the m.l.d. is about 2 x 10^{-7} grams/kilo or 2 x 10^{-5} grams for a 220 lb. man. That is, 0.00002 gms. (two one hundred thousandths of a gram) will kill a person of that size. One gram is sufficient to cause 100,000-200,000 deaths. A 350 lb. batch of the culture medium, i.e., a 35 gallon carboy or a 50 gallon oil drum could contaminate a 10,000,000 gallon reservoir so that, if evenly dispersed, every 5 cc. unit of water could be a m.l.d. for humans.[5]

The toxin resists the action of digestive acids, is highly stable to desiccation, is heat resistant, and the attack rate, i.e., susceptibility to the poison, is 100%.

One disadvantage to the use of botulinus toxin is that the epidemic is self-limiting. The disease is a poisoning and no infection is involved. One case does not lead to another, for the toxin does not propagate itself. Hence, there can be no secondary cases. However, the difficulty of preventing this disease if a serious attempt is made to introduce it, points this disease as one of the most dangerous and important B.W. agents, especially for poisoning reservoirs.

Serum therapy, if the antitoxin used is active against the A, B, E, and other types of toxin, is useful in treatment.

The presence of botulinus toxin in water (or food) is determined by injecting white mice. Symptoms develop in 3-4 hours. Under conditions of acute international political tensions, a prophylactic system should be instituted wherein all waterworks engineers would be required to keep a colony of mice on hand, inoculate them at frequent intervals, and wait for the normal prodromal period before passing the water into the lines. This holding period would be a difficult operation under the waterworks systems now in use.

2. *Bacillary dysentery.* Caused by *Shigella* spp. This disease is also insect-(fly) borne and has been discussed previously in the preceding paper (Elisheswitz, 1951). However, it should be pointed out that it is also an important B.W. agent. Its incubation period is very short (24-48 hours) and although most strains only cause a severe transient

5. The crystalline botulinus toxin has a potency of 30,000,000 m.l.d.'s/milligram for mice. Thus, one ounce contains 90 billion m.l.d.'s for mice or 180 million m.l.d.'s for humans. This is 20 times the potency of the most concentrated broth extracts. One ounce of the crystalline toxin is sufficient to eradicate the total population of North America. For B.W. purposes, however, the broth toxin is sufficient. The crystalline toxin can be used for immunization as immunizing toxoids.

(a few days) incapacitation, some, like the *shiga* type, are fatal. A high percentage of the people can be easily infected and reinfected, and secondary dissemination is easily established. It spreads like wildfire and leaves the populace prostrate. The vaccines are toxic themselves and there are too many different antigenic types to permit the development of adequate vaccines. It is easy to cultivate in large quantities with simple equipment, and hence, it makes an attractive B.W. agent for saboteurs through contamination of water, milk, or food.

Fly-borne outbreaks have been particularly severe in armies. The convalescent carrier rate is high (30%) and the organisms are excreted in the feces.

Antitoxin therapy is reported to be effective; although as yet no antibiotics have proven successful in treatment, the sulfonamides work adequately and no antibiotic treatment is required.

3. *Poliomyelitis virus.* This virus is capable of being transmitted by water and food-borne routes; it is resistant and its use would strike great psychological fear. However, the difficulty in culturing the virus in large amounts and the low degree of symptomatic pathology in the adult population, preclude its use.

4. *Brucellosis.* This disease complex (three species and many strains), although normally transmitted by eating and handling meat, milk, and hide products of cattle, goats, and swine, is also capable of transmission by the air-route. The latter seems the more dangerous and probable mode in B.W., hence the diseases will be discussed in that section.

In the *water-borne contact* diseases, we find leptospirosis and schistosomiasis.

The introduction of the cercariae of *Schistosoma* spp., through the intermediary of infected snails, into swimming pools, lakes, and rivers is a possibility but its use is improbable for a variety of reasons.

The use of *Leptospira icterohemorrhagiae*, the causative agent of leptospirosis, however, would be worthwhile; this because the disease is a prolonged and prostrating illness with a high fever, short incubation period (one week), easy cultivation of the organisms, the lack of a commercial vaccine, and the difficulty of treatment. In animals most of the antibiotics are effective; in humans, the reports have not been as encouraging. However, the organisms are sensitive to changes in salt content of water and their attack rate in man is low. In nature, transmission is effected by water contaminated with rat urine. In B.W., the water can be artificially seeded. Its use as a field weapon against troops rather than cities is the more probable.

Methods of Artificial Dissemination of the Food- and Water-borne Diseases.

While it is possible that airplanes might be used to seed the reservoirs or other water supplies and crops with these water and food-borne infections, it is most probable that sabotage will be resorted to instead. In the former attempts, our present sanitary safeguards will go a long way toward preventing any such outbreaks; in the latter, we are wide open. Milk, ice-cream and dairy supplies, breweries, soft-drink plants, canneries, and swimming pools, and water-treatment plants, all industries which have a widespread consumer contact, can be seeded by saboteurs with any of the toxins or organisms after the final sterilization stage and just before the product is bottled, packaged, or put into the pipelines.

In the past war, in some sections, precautions were taken to prevent this type of sabotage: no visitors were permitted in water-treatment plants and all employees were screened by the F.B.I.; the reservoirs were patrolled by armed guards; and ice-cream and bottling plants in the Canal Zone and other areas which made their products mainly for the Armed Forces were staffed and operated by military service men. It is obvious that if any serious attempt were to be made to carry out B.W. with any of the enteric organisms, these defenses could be broken through or a way found to circumvent them. The alternative would be a complete militarization of every phase of the food, drink, and water processing industry.

B. *The Contact Infections.*

Three groups of diseases fall into this category: 1) the direct contact venereal infections; 2) the direct and indirect contact parasitic and fungal dermatoses; and 3) the indirect contact wound infections.

1. *The venereal diseases.* Since these are transmitted exclusively by venereal contact, there is no need of artificial B.W. introduction of these organisms. The reservoirs are already among us and the morbidity rate is as high as it will probably get even if the enemy parachuted a carload of infected blondes into our midst. Fox (1933) stated, "The soldier's danger from venereal diseases will not come from the open, avowed, wartime enemy who love him the least, but from the money-loving or uniform-loving ladies who profess to love him the most."

2. *The parasitic and fungal dermatoses.* These have been discussed under effects of atomic bomb attack. Since the reservoirs are already among us, there is no need to introduce additional sources. Spread depends more on general sanitary conditions than on what an enemy can do in B.W.

3. *Indirect contact and wound infections.* This is a large and heterogeneous group of diseases. It includes: 1) many of the superficial mycoses; 2) some staphylococci and hemolytic streptococci infections, e.g. erysipelas; 3) diseases caused by spore-bearing bacteria, e.g. anthrax, tetanus, and the gas gangrene group; 4) infections caused by animal bites, such as rabies and rat-bite fever; and 5) infections which result from contact with animals, e.g. brucellosis, glanders, tularemia, and melioidosis. These are all capable of transmission by other routs. Most of these can be dismissed from consideration.

1. The superficial mycoses such as athlete's foot and epidermophytoses, although of considerable military importance, as witnessed by the high incidence, are already among us in a high proportion of the civilian population. The areas are already well seeded. The infectivity rate is high, but the transmission and infection depends on other factors such as footwear, community living, dryness of feet, etc., over which the enemy has no control. Hence, they are unlikely to be used as B.W. agents.

2. Attempts to induce furunculitis, carbuncles, erysipelas, etc. by artificial means, such as inoculating cosmetics before they are packaged, are possible, but not probable.

3. The diseases caused by the spore-bearing rods like anthrax, tetanus, and gas gangrene are all capable of being transmitted by air-borne infection. In this lies our greatest danger and hence they will be discussed under air-borne infections. It can be pointed out, however, that it is entirely feasible to impregnate the spores of these organisms onto an inert clay talc and disperse them in anti-personnel mines, bombs, and shells, so that as the steel fragments scatter, the individuals hit or even scratched with shrapnel will be inoculated. Natural shrapnel wounds are likely to be contaminated by *Clostridium* anyway and the increased percentage of positive gas gangrene cases resulting from artificial seeding may not be worth the effort. Also, in those areas where the soil is dry and receptive, it is possible to seed the soil with spore-laden gelatin capsules. When the capsules disintegrate, rain will spread the spores and thoroughly seed the soil.

4. Animal bite infections can also be dismissed. The attack rate of the vector animals is too low and the infectivity rate is also low. In addition, rabies appears to require a deep parenteral administration.

5. The animal contact diseases, such as glanders, are all important but will be discussed under air-borne infections since this is their most likely means of spread. It is unlikely that any other means of B.W. will increase the present rate of these diseases.

C. *The Air-Borne Infections.*

Air-borne disease agents as a group are of greatest potential usefulness because of the ease with which they can be disseminated and the relative impotence of standard sanitary measures against them.

Many disease agents can be disseminated in more ways than one; e.g., polio-

myelitis, while usually considered a respiratory or air-borne infection, can be transmitted through feces and urine-contaminated water and food. Many organisms are even more highly pathogenic when transmitted by these "unnatural" routes; e.g., hemorrhagic smallpox, anthrax, plague, staphylococci, etc., are all highly pathogenic when transmitted to the respiratory system. It is now considered that nearly all of the communicable diseases can be air-borne and contacted by the respiratory route and are, thus, potential B.W. agents. Most of the causative organisms have been shown experimentally to be adaptable and can cause primary infections. Their actual use would depend on the criteria of suitability enumerated previously. If, after primary infection, the cycle can be kept going by one individual infecting another, so much the better, but this may not be necessary if the number of primary cases caused is sufficient to fulfill the purpose of the attack.

One of the easiest methods of determining just what microorganisms would make useful B.W. agents is to study the record of accidental laboratory infections among personnel working in the laboratories. Pipetting of solutions from one tube to another and the use of motor blenders such as the Waring Blender for tissue homogenates cause minute droplets of infective spray to be thrown into the air where they are inhaled. Such a study provides clues to the properties of the disease agents: high infectivity for man and air transmissibility, or the ability to cause infection when inhaled into the lungs. Such diseases as anthrax, plague, glanders, tularemia, brucellosis, typhus and other rickettsial diseases, yellow fever and other virus diseases which are not normally in nature air-borne, have shown themselves by these laboratory infections to be adaptable to this means of transfer.

The classic example of how this study was applied to yellow fever is a demonstration of the development of a good potential B.W. agent. In nature, the disease is mosquito transmitted. Some 34 reported cases of laboratory infection from 1898 to 1945 had nothing to do with mosquitoes. Some followed only a single exposure to cultivated dessicated virus, and one was in a visitor who passed through the laboratory only once. This means that yellow fever has the two important B.W. characteristics of air transmissibility and high infectivity for man. But yellow fever is not a respiratory disease; a person who has it does not cough or sneeze. The B.W. workers first pointed out its possibilities of spread through the air, as aerosol clouds or put into the air conditioning systems of public gathering places, in temperate and cold climates where respiratory illnesses flourish. The virus is easy to cultivate and propagate in large quantities. Although there is a suitable vaccine against the disease, it would be almost impossible to vaccinate the entire urban population. Three immunizing injections are required at weekly intervals. It would take 50 teams of doctors and technicians (250 people) vaccinating 50,000 people a day over 200 days to vaccinate the population of Chicago! Besides the lack of sufficient vaccine, the same procedure would have to be repeated for all the other diseases in the potential air-borne list, where adequate vaccines have been developed.

Two other conditions should be kept in mind. Some of the agents which have a low infectivity rate when inhaled into a normal intact lung, may find a ready harborage and become highly infectious if the lung is mechanically wounded or has open lesions of any sort. The previous or the concomitant use of SO_2 or a Cl_2 fog to irritate the nasopharyngeal mucosa and lung epithelium might well be used to set up a receptive substrate for the B.W. agent. The use of two or more organisms at the same time, utilizing the principles of synergism, may well be resorted to.

In considering the following list, to get the full import of the picture, the facts already alluded to should be kept in mind: a) genetic selection has increased the virulence of most of the communicable disease organisms; b) these organisms are almost all capable of being air-borne and setting up infection via the respiratory tract; c) such diseases are

usually more severe to treat; d) efficient equipment and methods are available for the widespread dissemination of these agents; e) more than one organism may be used; f) it is futile to try and vaccinate the whole population against all the potential B.W. diseases.

This leads to only one conclusion. As Piel (1946) pointed out, "There are no by-paths to the issue of biological warfare. *The only way to control biological warfare is to prevent war itself.*"

The list of diseases which can be spread by the air-borne route is an imposing and heterogeneous one, including viruses, rickettsiae, pleuropneumonia cocci, bacteria, and fungi.

The most important of these to man are the following: anthrax,* brucellosis,* coccidioidomycosis,* common cold, dengue, diphtheria, equine encephalomyelitis and other encephalitic viruses (e.g. St. Louis encephalitis), foot-and-mouth disease, Friedlander's pneumonia,* glanders, influenza (virus with *Hemophilus influenzae*),* louping ill, measles, melioidosis, meningococcus meningitis, mumps, pasteurellosis (hemorrhagic septicemia, pneumonic plague,* psittacosis,* Q-fever,* rift-valley fever, rinderpest (mainly on cattle), smallpox (hemorrhagic type),* streptococcal pneumonia,* tetanus, tularemia,* yellow fever.*

Of these, the asterisk-marked diseases appear to be the most dangerous. We will here note only a few salient points about them.

1. *Anthrax.* Normally contracted through skin contact as a skin infection from handling cattle hides or infected meats, as a respiratory infection it is very serious. It results in a severe and intractable pneumonia. Penicillin, however, is an effective treatment. The fact that the spores can be produced easily in large numbers and are extremely resistant to desiccation makes this disease a prime B.W. weapon.

2. *Brucellosis.* Of the three main varieties, *Br. melitensis* appears to be the most infectious. All, however, cause a chronic, debilitating illness which leaves the patients exhausted, depressed, and with progressive neuralgic symptoms. The incubation period is relatively short, being as short as one week. The organisms are capable of prolonged survival in the open environment. They retain their viability for 2 or 3 months in the dry dust which impinges on clothing. The disease is mainly a septicemia without involvement of the respiratory tract, and the patient does not contaminate his environment. No high degree of epidemicity or secondary spread of the disease appears likely. Adequate vaccines and antibiotic therapy are available.

3. *Coccidioidomycosis.* This dust-borne respiratory fungal infection occurs endemically in arid regious of the Southwestern United States, South America and other areas. Efficacy of the transmission by the highly resistant spore stage, the arthrospore, is shown by the fact that a high percentage of the population of some areas is, or has been, infected with the primary form of the disease, a benign, self-limiting respiratory infection, even after only short exposure. The chronic, malignant, disseminated form, which involves cutaneous, visceral, and osseous tissues, is normally found in only a low percentage of the cases. The danger exists that this organism, or those of other similar deep-mycoses, can be modified experimentally so that its invasiveness is increased and a higher percentage of the debilitating metastatic phase of the disease results in infected patients.

4. *Friedlander's Bacillus* (*Klebsiella pneumoniae*). Normally this organism causes a pneumonia which depends on predisposing factors — fatigue, respiratory infections due to other agents, etc., before it takes hold. It then causes a highly virulent pneumonia. Newer strains have developed which are more pathogenic and which are also highly resistant to the usual antibiotics.

5. *Influenza.* Due to its highly infectious character, the high morbidity rate, and the probability of secondary spread, the use of egg or tissue-cultured influenza virus, used either alone or in conjunction with bacterial or other viral agents, such as *Hemophilus influenzae*, readily suggests itself. Dried virus on domestic fomites, house dust, or other materials retains its activity for some

time. Large scale pandemics of the disease have, in the past, caused great dislocation of normal civilian activities and commerce. Since there is no adequate therapy nor universal multi-strain vaccine available against influenza, this disease ranks high on the list of potential B.W. agents. The danger of retroactivity, that is, the epidemic once started might develop into a pandemic which attacks the population of the user's country, is a strong deterrent to its use.

6. *Pneumonic plague.* A particularly pathogenic form of *Pastuerella pestis* has been produced. Stable in the air, it lends itself for mass air dissemination. The result is the most severe form of plague, pneumonic plague. The dissemination from primary cases to secondary cases is rapid. Streptomycin is effective in treatment.

7. *Psittacosis.* Highly virulent strains of this virus have also been developed and can most easily be disseminated through air-conditioning systems and central air inlets. It is one of the most useful B.W. agents because it has an infectivity rate for man of almost 100%, is highly pathogenic, can be readily cultivated, and retroactivity is controllable by vaccination. A high percentage of those who handle the disease in the laboratory become infected. Aside from these laboratory infections, the other reported cases are associated with contact with birds, particularly parrots and parakeets. The disease is a severe pneumonitis which leaves the patient in a debilitated condition for long periods of time or for life. Diagnosis is difficult. Complement fixation tests must be resorted to but become positive only after a week or two. Aureomycin and penicillin can be used in treatment.

8. *Q-Fever.* This rickettsial infection has, in the past, been associated mainly with stock-yard workers, milk handlers, and others who handled cattle products. It is common among workers in Australia and California. Recent reports have shown it to be almost world-wide in distribution. Its symptomatology is protean and the disease has been masked under a variety of other conditions. However, in many cases it leaves the infected individual debilitated for a prolonged period of time.

9. *Smallpox (hemorrhagic type).* Highly virulent strains of smallpox have been developed which cause a hemorrhagic type of disease and pneumonitis. Ordinary vaccination protects against this form of disease. However, although most of the population have been vaccinated in childhood or before entering school, there is a high percentage of non-immunes in the population, adults who have not been vaccinated for 5 or more years, children, etc. The use of this virus, then, will hit all levels of the population. The virus can be grown easily on minced mouse embryo in tissue culture or on chick eggs, and dispensed as an aerosol.

10. *Streptococcal pneumonias.* Strains have been developed which are completely resistant to the known antibiotics. This, plus the fact that streptococcal pneumonias have always been sèvere and pernicious, makes their B.W. use attractive and menacing. The *staphylococcal pneumonias* perhaps should also be considered. They, like the streptococcal pneumonias, are particularly pernicious.

11. *Tularemia.* The tremendous amount of study given this disease and its causative organism during the past decade is ample testimony to the inherent dangers in its use. It is highly infective, one single *Pasteurella tularense* organism being capable of causing an infection. It is highly virulent, producing a prostrating disease and a prolonged disability after a short incubation. The organism can be adequately protected to resist desiccation and the action of physical and chemical agents. Although normally transmitted by insect and tick bites or by contact with or ingestion of infected animals, or contaminated natural waters, infection by inhalation and directly through the unbroken skin and conjunctiva is also possible. The possibility of tularemic pneumonias developing, especially after inhalation contact as the primary source, should be kept in mind. This might result in secondary pneumonic transmission. Adequate antibiotic therapy is available against the

ordinary non-resistant strains of the organism.

12. *Yellow Fever.* This has already been discussed as an illustration of the use of an air-borne B.W. agent. Some of the other viral diseases and viral encephalitides, e.g. dengue, rift-valley fever, equine encephalomyelitis, Japanese B encephalitis, and the large series of other meningoencephalitides may be similarly adaptable.

Methods of artificial Dissemination of the Air-Borne Diseases. Because of the comparative ease with which they can be disseminated and the relative impotence of standard sanitary measures against them, the air-borne disease agents are of greatest potential usefulness in B.W.

The primary dissemination of any of these air-borne or respiratory diseases can be made in three ways: by airplane distribution of contaminated aerosols; by introducing the contaminated aerosols into the air-conditioning systems of theaters and other public gathering places; and by introducing the organisms into the air intake systems of the subway systems and tunnels. Since everyone breathes, everyone in these confined areas is reasonably certain of inhaling the B.W. agent.

A few words about aerosols. An aerosol is defined as a suspension of a liquid in a gas (air) in which the particle sizes of that liquid are between 0.5 and 10 microns. This makes the size range between that of smoke and minute spray particles. This size range has many advantages. It is easily produced by a variety of means, thermal or mechanical, and the particles are fairly stable. They tend to settle very slowly and remain suspended in air for a sufficiently long time. Smokes, on the other hand, which have particle sizes of 0.001 to 0.5 microns tend to rise with inversion currents caused by differences in temperature between the earth and the air or between an object (or body) and the air. They are too dependent on wind currents, stay suspended too long, tend to rise, and may not settle on anything. Visible spray droplets, on the other hand, settle too rapidly and are not carried far enough by the wind.

A wide variety of suitable large-scale machines have been developed for the production of aerosols. These machines may be either truck mounted or plane mounted; some are complex and some are simple. One of the most efficient methods for producing aerosols is to merely pump oil in which the organisms are suspended under low pressure through a fine orifice which opens into the hot exhaust air stream of the muffler of a plane or car engine. The momentary contact with the heat vaporizes the oil into aerosol droplets without destroying the organisms or chemicals. Mechanical methods involve the mechanical breakup of an oil or water mass by spraying against a revolving plate or even spraying out of a fine orifice under high pressure. The smoke-generators used by the Army and Navy for smoke screen deposition can be modified to produce aerosols. The familiar insecticidal "aerosol bomb" or aerosol paint dispensers work on still another principle—the refrigerant gas, freon, which is under pressure and liquified in the container, is allowed to expand through a fine orifice of the outlet tube. As it does so, it vaporizes into a gas. The pressure release causes the liquid contained inside the bomb to be ejected as a fine aerosol spray. The physics and mechanics of these instruments and droplet size regulation is a complex science but has been well worked out. Besides their potential use in bacterial warfare, aerosols are widely used as insecticide applicators for crops, are used for both chemical warfare and smoke screen depositions, for air sterilization, and have many chemical industry uses for washings of acids and oils.

An additional advantage of aerosol production is that a little liquid goes a long way. The total surface area of the droplets has a geometric ratio to the inverse of its diameter, and 1 cc of liquid can be broken up into billions of aerosol particles.

Almost any of these aerosol producing apparatus can be used to disseminate any of the B.W. agents. The organisms are suspended in an oil or other liquid of suitable specific gravity and non-tox-

icity (e.g. glycerine) and run through the machine. The myriads of minute droplets will all contain some of the infectious organisms.

It is quite feasible for fast-flying airplanes to lay down dense bacteria-loaded aerosol and smoke clouds over cities and troops to set up the primary infections. These clouds will settle like a smoke screen over the area below and the wind drift will carry the particles further afield. Utilizing the principles of smoke-screen deposition, it is not at all unlikely that a whole fleet of planes could come over in staggered formation to blanket an area completely at once, so that the discrete clouds of areosol as laid will finally fuse into a solid blanket.

However, this is not the only way that the air-borne organisms can be spread. Aerosol can be released into the air conditioning systems of movie theaters, large office buildings, auditoriums, industrial plants, etc., much as aerosols of triethylene glycol are now released in attempts to sterilize the air of these places and cut down on respiratory diseases. In addition, vehicular tunnels and subways also offer tempting outlets. They draw their air in from central air inlets, or, if there are many air ducts, at least the area is a confined space. The aerosol or spray can either be released into the air inlets or the tunnel itself can be sprayed. Autos or trucks with quiet, practically smokeless, exhaust pipe venturi generators could drive through city streets, quietly spraying the populace, much like flies have been sprayed with DDT insecticidal aerosols.

D. *The Vector-Borne Diseases.*

This heterogeneous group of diseases can be classified into: 1) the flea and louse-borne group; 2) the mosquito-borne group; 3) the tick and mite-borne group; and 4) the fly and gnat-borne group.

Under certain conditions, especially in the tropical or subtropical areas, among troops deployed in the field, or in rural areas, some of these might be of great importance to man or his livestock. Among urban populations, especially in a city like Chicago, many of the diseases can be dismissed from consideration. With but few exceptions could the introduction of these diseases via infected vectors cause a high morbidity. Their main value would be a nuisance value, which is not the purpose of B.W.

1. *The flea and louse-borne diseases.* This group, which includes endemic or murine typhus, trench fever, plague, epidemic typhus, epidemic relapsing fever, etc., has been mentioned previously (Elishewitz, 1951). Although normally transmitted by very different types of insects, epidemiologically the diseases have many characteristics in common. They are highly epidemic under suitable environmental conditions—crowding, gross insanitation, and lack of personal hygiene. They are diseases of poverty and the social disorganization which accompany wars.

The louse-borne epidemic diseases, relapsing fever, trench fever, and typhus, can be passed over quickly. If social conditions are appropriate for their development, they are likely to appear and spread without artificial seeding; if such conditions are absent, no severe natural epidemic will result. Among border areas or troops in the field, it is possible to introduce a reservoir of infected lousy individuals by means of returning prisoners or refugees. Modern insect control delousing programs utilizing DDT dusts can bring any outbreak under short control.

The problem is more serious in the flea-borne endemic typhus and plague. Here the insects feed mainly on rats and the diseases are primarily diseases of these rodents. Transmission to man is secondary. However, the rats and their fleas are already with us in all urban areas. Infected urban plague reservoirs are absent in the United States, but are plentiful in the campestral areas of the West; urban endemic typhus is absent in the Northern United States but plentiful in the Southern United States. It would be feasible to seed urban areas with plague-infected rat fleas and thus introduce the disease into the rat population, but whether a fatal epizootic would take place among these rats and secondarily carry over to humans is problematical. It depends on a complex interaction of epidemiological considera-

tions involving climatic conditions, social disorganization and poverty, rodent populations, etc. In any event, as pointed out above, typhus and plague can also be air-borne diseases of some B.W. importance, and this method of dissemination is probably preferable.

2. In *the mosquito-borne diseases,* malaria is of great importance for troops deployed in tropical areas; in the northern urban areas it can be neglected. Dengue, a virus infection of high infectivity and debilitating power, can incapacitate masses of troops or civilian populations in a short period of time. It might be important if Chicago had a larger indigenous mosquito population, but, as pointed out previously, mosquito breeding is seasonal and in the city is too low to maintain this disease endemically or epidemically. Mosquito breeding in water catchment areas or flooded basements where water is stored for emergency fire-fighting supplies in event of atom-bomb attack, forms a potential danger source. Yellow fever and the other viral encephalitides have already been discussed. Filariasis would not become established through introducing infected vectors; infected reservoirs are required.

3. *The tick and mite-borne group.* Of the wide variety of rickettsial, viral, and spirochaetal infections transmitted by these arachnids, none is contagious. All have animal (small mammal) reservoirs. Transmission to man is accidental and sporadic, and none is apt to become epidemic in urban areas, where contact between man and ticks or mites is limited. In Rickettsial-pox, wherein house mice are the reservoirs and their mites are vectors, the disease is already endemic in many cities. It is difficult to conceive how the rate could be increased by enemy-imposed means. The hard ticks, which feed only once during a stage are, moreover, under a handicap of reduced transmission potential. Several of the diseases, e.g., Q fever, equine encephalomyelitis, etc., are capable of being air-borne and air dissemination would be much the preferred route of use in B.W.

4. *The fly and gnat-borne group.* Most of the other insect-transmitted diseases fall into this group. The majority of them, such as the protozoan leishmaniases and trypanosomiases, can be dismissed on the ground that the ecological requirements of their vectors are too exacting to permit their becoming adapted to urban conditions. The fly-borne bacterial enteric infections were discussed in the preceding paper on atom-bomb problems. The house-fly and most of the enteric infections are already endemic. Little benefit would result from introducing other flies. Introduction of the disease organisms, like cholera, via food or water has previously been discussed.

E. *The Endogenous Group.*

This last includes diseases like subacute bacterial endocarditis due to *Streptococcus viridans,* Vincent's angina and related oral infections, and Actinomycosis. These are diseases in which the transmission of the infective agent through the environment is of secondary importance in their inception. Their pathogenicity depends on predisposing causes in the host. Hence, this group are of little consequence in bacterial warfare.

Control Measures in Bacterial Warfare.

Just as abstinance is the only certain method for prevention of pregnancy, so world peace is the only certain method of preventing the ravages of B.W.

Control methods for the food and water-borne organisms were indicated in the section discussing that problem; there is little likelihood of contact, endogenous, or arthropod-borne organisms being used. The problem, thus, in control involves only the air-borne groups.

One main personal prophylactic measure, of course, immediately suggests itself—the use of an all-purpose, chemical gas, bacteria and virus-proof mask. A variety of types has been designed, some more comfortable than others, but the practical problem of educating a population to wear them or carry them constantly during wartime is difficult. None of them is pleasant to wear. Application of B.W. attack via airplanes might give warning and the masks could be used; sabotage application from ground apparatus, however, would catch the populace without their masks.

(Cont'd on page 155)

THE DEVELOPMENT OF PRENATAL BEHAVIOR*

R. FREDERICK BECKER, Ph.D.**

Development of behavior is a broad subject, and I can touch on only those aspects of it which pertain to the initiation of early motor functions in mammalian embryos, if I am to remain within reasonable limits.

Really concerted efforts to determine how the nervous system of embryos begins to function started some 20 years ago. They followed a series of reports on the genesis of behavior in amphibian embryos by Coghill, who coupled his functional observations with detailed histological studies on the developing nervous system. By the late '30s, several investigators had issued reports on mammalian fetuses. Minkowski in Switzerland and Bolafio and Artom in Italy had assembled significant numbers of observations on human embryos. Barcroft and Barron in England had studied sheep fetuses. In this country, work had already been done by Swenson and Angulo on rat fetuses. Coronis, Windle & Griffin had reported behavioral observations on cat and guinea pig fetuses. Hooker, and Windle & Fitzgerald were able to study human fetuses. It was about this time that Windle and I began to re-investigate the whole problem of early prenatal motility in light of the physiological conditions that obtain *in utero*.

I suppose our greatest contribution was to point to the necessity of limiting interpretations of observed behavior to the physiological conditions imposed by any given experimental environment. All behavior is but the overt expression of all environmental factors, intrinsic and extrinsic, which are operating in the life-space of the organism at the given moment of observation. One can consider genetic or hereditary factors as part of the intrinsic vectors in the life-space of the individual. Such a generalized concept as this is applicable on adult levels as well. One might well ask, "What about factors such as memory and the subconscious, which seem to act out of the past to motivate the organism in the present?" Memory has been characterized structurally as a closed system of reverberating neuronal circuits. Its overt existence is made known at a given moment only when present sensory impulses break thru to rechannel the circuit to some motor outlet. Even those fuzzy unconscious factors which our psychoanalytic brethren allege lie hidden as impressions from early prenatal or postnatal infancy, but which motivate us in our aberrant actions as adults, do not act from the past, but in the very present to make us do what we do at the moment. Dredging them up from the past for an airing is not important. It is the realization that something in our present external environment is channeling ancient neural circuits, present even now in our internal make-up, to act as vectors of force which makes overt behavior understandable to the observer.

The line of reasoning just presented has all the ear-marks of a tool borrowed from Gestalt psychology. It is ironic that it should be put to use to refute a Gestalt concept of the genesis of behavior in the mammal.

A basic tenet of Gestalt psychology is that the whole is greater than the sum of its parts. Atomistic analysis of segments of behavior always fails to achieve a satisfactory explanation of behavior. Thus the synthetic approach is favored over the analytic. Gestaltists have pointed with reasonable pride to Coghill's interpretation of genesis of behavior in that urodel amphibian, Amblystoma. And well they may, for a more careful and painstaking study has probably never been done. Here is evidence that the earliest fetal behavior begins as a total pattern of mass activity. All parts of the organism are involved in its early motility, and only later are more precisely localized movements individuated out of a gross

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total pattern. This is a satisfying statement of the fact that the whole is greater than the sum of its parts even from the very beginning.

From what we know about the intrinsic organization of its nervous system when motility is first observed, and from what we know about its bodily development at the time, and from what we know about the external environment of Amblystoma, the facts fit a total pattern theory nicely. For Amblystoma, it represents the exact status of behavior at its earliest inception. The life-space of this organism is so structured and the vectors of force so oriented that its resultant behavior must be manifested in this manner and in no other if Coghill's findings are correct.. That this is true, does not necessarily prove that it must be so in the developing rat as Angulo tried to show (contrary to Swenson's findings), or in the human as Minkowski, Bolafio & Artom, and Hooker tend to intimate.

Windle and I suspected that all of the early work on mammalian fetuses was open to criticism. There was no instance in which it had not been conducted under unphysiologic and abnormal conditions—indeed on deeply anesthetized and often dying fetuses. Little was known about the intrauterine physiology-factors in the very milieu in which the organism was developing. Nor were the investigators concerned in controlling their artificial experimental environment—the milieu in which they placed the organism when they made the observations. Narcotic and anesthetic drugs which depress and abolish precisely localized reflex activity were frequently employed. The effects of these agents were blithely ignored in interpreting the so called "normal" behavioral pattern. Even though Minkowski was careful to use local anesthesia on the mother so as not to depress fetal activity, his young were delivered from the womb free of their maternal blood supply and studied in another room under conditions that deprived them of their normal temperature and balanced aquatic environment. This was done at a critical time when the very livelihood of the organism depended on these factors. Developmentally neither its respiratory, circulatory, nervous nor sensory mechanisms were ready to cope with such an artificial milieu. Its behavior therefore could only be an altered response to altered conditions. Similar criticisms can be leveled against Hooker's studies on human fetuses.

These factors are extremely important, for even a delay of a few minutes in making observations after incising the uterus invokes the danger of reporting on what is occurring under anoxic stress. The desideratum is to approximate conditions as they exist *in utero* and to report observations under those conditions alone as "normal." One then describes other behavior as altered by the factors operating at the moment. For it is the vectors of force acting in an organism's life-space at the moment that give the resultant of its behavior. This is sound topological geometry and should appeal to the most ardent of Gestaltists—like the Lewinian School at Massachusetts Institute of Technology. (It is indeed interesting to see how the mathematical-minded gentry of M.I.T. are creeping into neurological circles lately, e.g. also Norbert Wiener of Cybernetics fame. And a healthy sign it is, too!)

Hence we set about re-evaluating the development of fetal behavior under conditions most nearly approximating life *in utero*. Anemic decerebration was performed on pregnant mothers when cats were used. An hour or more elapsed to allow the maternal animal to rid itself of the effects of the anesthesia before the uterus was incised and the fetuses were shelled into a constant temperature bath. The salt concentration of the bath was balanced ionically so that conditions again were comparable to those obtaining *in amnio*. The placental circulation was maintained intact in all experiments unless we wished to describe changes of behavior due to interruption of this circulation. So, early in all experiments, the fetuses had adequate and normal oxygenation. In the case of the guinea pig, we infiltrated the abdomen locally with procaine and cut through the anesthetized wall of the wakeful mother. In humans, observations were again limited to cases of mild sedation and anesthesia,

and placental circulation was maintained. Such material for study was made available at the operation site in cases involving necessary hysterectomy.

Significant species differences appear in the course of development of somatic activity but in the early stages of development of rat, guinea pig, sheep, cat and man remarkable similarity of behavior exists. Enough so that certain generalizations may be permissible.

It is convenient to classify progress in the genesis of behavior under three categories:

1. Myogenic responses.
2. Neuromotor responses.
3. Reflex responses.

Concerning the first two of these, there is little significant disagreement present among the observations of various investigators. It is over the third category that a clash of ideas is precipitated.

Somatic motility is present in all species before the body form has taken on the characteristics of the given species. That is, activity is first observed during the period of the embryo before the organism enters into its fetal period of development. This period varies naturally with the gestation time of the organism (Table I). But even the human at this time (7th week) looks not much different morphologically from the rat or cat in a similar stage of development.

Before muscular contraction can be induced in such an organism by nervous activity, muscle is capable of responding on its own. Indeed, spontaneous muscle twitching has been described in fish and bird embryos long before a nerve supply had developed. This is not a strange situation at all. Such non-nervous myogenic contractions have been known to occur in smooth muscle as well. Muscle of the amnion of the chick constantly contracts rhythmically though it is always devoid of nerve. In the chick this amniotic contraction must be reckoned with in descriptions of early behavioral development. Apparently the amniotic activity depends upon some change in smooth muscle itself or in the medium surrounding it. In the developing chick, the amnion becomes progressively more active during the course of incubation up to the 13th day of life. After that, amniotic contractions cease. Cessation coincides with the time that the carbon dioxide content in the air space of the egg reaches a high level. A condition of partial anoxemia exists which is physiologic in the chick egg. At this time, too, the chick squirms actively in the egg. Its behavior is of the mass type so accurately described by Zing Yang Kuo. Gestaltists have regarded this as another example of a normal total pattern of response. What else can an anoxic nervous system do under the early stimulus of carbon dioxide, but discharge massively? If observations are carefully made before the 13th day, it can be demonstrated that the chick is capable of executing clearcut, precisely localized limb and head responses just as in the mammal. One must be sure that these observations are not obscured by the rocking of the chick as the amnion contracts rhythmically. Precise responses in the chick make their appearances before the period of physiologic anoxemia. In birds one must take into account the changes that occur in the air space at the end of the egg which is, indeed, the avian placenta. Thus we see, that even in the bird, mass activity is not a primary type of response.

TABLE I.

Species differences in age and size of specimens at inception of somatic motility.

Species	*Gestation Period*	*First Movements* (Days)	*Size* (mm.)
Rat	21 days	15—16	12—13
Guinea pig	67—69 days	25—26	17—18
Cat	65—67 days	23—24	13—14
Sheep	21 weeks	33—34	24—25
Man	38 weeks	54—60	22—24

Likewise, in the fish and chick the spontaneous twitching of non-innervated somatic myoblasts precedes reflex activity. The twitching simulates that seen in muscle in tissue culture. No comparable phenomenon has ever been observed to occur spontaneously in skeletal muscles of mammalian embryos, under normal physiologic conditions. But when young cat embryos are removed from the uterus this phenomenon can be demonstrated under artificial conditions. So long as the embryo lies in a medium containing sodium, potassium, and calcium in the concentration of Locke's solution nothing happens. But change the concentration of one of these chemicals and spontaneous twitching of skeletal muscles ensues. Rhythmic waving of the tail and limbs is first noticed for here diffusion can take place most readily. Soon other muscle masses are brought into play and activity continues even after the embryo is cold and pale and its heart has practically stopped beating.

One can also elicit direct muscular responses in the intact organism at this early stage by stimulating the muscle masses directly with micro-electrodes. But the quality of muscular response is not at all like that which one sees after neural reflex mechanisms have become established because:

1. A minimal stimulus gives a quick contraction followed by slow sustained relaxation.
2. Succeeding stimuli bring forth continual response with little signs of fatigue or latent periods for recovery.
3. Contractions are localized to the small area near the tip of the electrode. Moving the electrode slightly produces a variety of movements in different planes of space. The nature of response is not constant.
4. The muscle retains a high degree of excitability irrespective of great changes in metabolism. In fact, in specimens bled white these myogenic responses can still be elicited.

Thus, early myogenic responses are qualitatively quite distinct from reflex responses.

The second stage of development appears when it is possible to initiate contraction in muscle masses by stimulating their motor neurons at a time when it is still impossible to excite contraction reflexly through sensory stimulation. This is the stage of neuro-motor response.

Nerve endings of a primitive kind are present shortly after the period of myogenic response. Although it has been impossible to obtain *direct* evidence in young cat embryos that purely neuromotor responses precede reflex responses, indirect evidence is at hand. In older embryos, where reflex types of responses have become depressed under poor physiologic conditions, one can still test for neuro-motor responses. Normally stimulation of the skin in the forelimb region will give a backward and outward movement of limb in any number of embryos of the same age as the earliest form of reflex response. No other type of movement genetically precedes this one. Now, if one takes such an older embryo in which reflex activity has been depressed and pushes a sharp dental probe between, say, C_7 and T_1, the same type of response is again elicited. But when the cord is pierced at a higher level (C_4-C_5), a forward movement of the limb is made. This is a new movement which does not come into play reflexly until a later stage of growth. Apparently its motor component is already present, however, since its motor center can be stimulated directly. The sensory limb of the reflex arc for forward movement of the arm does not seem to be laid down as yet, for no amount of cutaneous stimulation ever elicits it in embryos of this early age.

The third step in behavioral development is characterized by the appearance of reflex responses. Reflexes are not present until sensory and motor neurons, simple nerve endings in the periphery, central connector nuerons, and functional synaptic central connections have been formed.

At this point, two divergent schools of thought about the genesis of behavior come into sharp focus. One school (Coghill, Angulo, and Hooker) believes that the more or less discrete reflex types of movement are late comers on the scene

and are not the primary units of behavior. Rather these local reflexes differentiate from a more fundamental background of massive movement. Hooker, in the human, and Angulo, in the rat, present observational data to support such a thesis.

So far Coghill has offered the only valid neuro-histological support for such a theory. It is unfortunate that the evidence rests on the structural pattern of an amphibian form. It is good and excellent evidence as far as it goes, but the jump from the amphibian to mammal, including man, can not be made on these premises. They do not fit in with the entirely different structural plan of the nervous system as we know it in mammals.

Windle, Carmichael and I sit on the other side of the fence. Our observations under the best of physiologic conditions, and our neuro-histological data, are in keeping with the idea that early behavior begins as a series of relatively simple reflex responses—entirely discrete and distinct from one another—which only later are built into a more complex reaction pattern by the progressive neuronal integration of these less complicated elements.

In the amphibian, Coghill found that a motor mechanism develops on each side of the embryonic floor plate as a longitudinally conducting system of neurons. Each neuron extends a process caudally to the next one below; from this process branches run to the segmental muscles of the back (and later to the limbs). This series of neurons constitutes an integrating motor system which is laid down before function appears. An integrating sensory system is next formed by temporary neurons, the Rohon-Beard cells, in the dorsal part of the spinal cord. They, too, send out long processes but in a rostral direction with branches running to muscles and epithelium. The motor and sensory systems become connected by commissural floor plate neurons which appear near the rostral end of the embryo (See Figures 1 & 2).

A stimulus applied to one side of the embryonic salamander sets up impulses which are conducted rostrally in the sensory system, across the rostral floor plate neurons, and then caudally in the integrating motor system. The whole organism bends in a C-shaped flexure toward the contralateral side. It is a mass movement or fully integrated response from the very start. Later, (Figure 2) through collateral branches of motor neurons which allow caudally flowing impulses from one side to precede those of the other, bilateral flexion and integrated swimming movements come into being. All this precedes, even, the development of limb buds. When the limbs appear they move passively with the trunk at first and only later acquire independence. Limb movements of a precise sort, then, may be said to individuate from the mass movement of the trunk. Thus we see that early development in the nervous system of the salamander is nicely correlated with its observed aquatic behavior.

Human and other mammalian embryos are so different morphologically from Amblystoma when movements and reflexes first appear that it is indeed surprising to find Hooker, Minkowski and others arguing for any functional similarity to a gross total pattern of this sort in mammalian forms. The larval salamander develops its total reaction and integrated side to side waves of movement before limbs or mouth have been formed. There never appears at any time a comparable chain of Rohon-Beard cells in the central nervous system of mammals. Motor neurons at first are only segmentally arranged in the cord rather than longitudinally as in the salamander. Interconnections are rare from one level to the next. The earliest secondary interneurons build predominantly ascending rather than descending pathways. Few descending fibers from the brain reach cord level at the time of inception of behavior in the mammal.

In other words, there is no longitudinal integrating mechanism in the cord of mammalian embryos at a stage of development which corresponds to the early motile Amblystoma—nor will there be until a long time after many other neural mechanisms have come into play. By the time structural advances make function possible, the head and limbs have become

prominent features. In the further course of development the head and limbs exert an ever increasing dominance over the trunk. There is no need at any time for an aquatic locomotor pattern such as is found in fish and amphibians. Even functionally it is not necessary for ontogeny to recapitulate phylogeny. C- and S-shaped trunk flexures have been observed in mammalian forms, but only under conditions of anoxic duress when all cells of the central system are stimulated to massive discharge.

One day to a week (depending on the species) after myogenic responses have been operating in mammalian embryos, early behavior makes its appearance. The description which follows is based on observations in the 14 mm. cat embryo, but similar results have been observed in other mammals.

When an embryo with its placental circulation intact is brought quickly into view and its amniotic sac is percussed with a blunt instrument, pressure waves, transmitted thru the fluid, bring about a quick outward and backward movement of the forelimb. Return to rest is equally abrupt. The movement is in nature of a clean cut twitch or jerk. No other part of the body is brought into play. The response can be elicited equally well by flipping the limb gently with a hair or needle thrust through the amnion. It is not readily elicited by touch alone since stretch receptors seem to be involved.

In the same embryo (14 mm. cat), stimulating the snout results in a head extension, and, when the stimulus is applied to either side of the mid-line, contralateral head movement *with extension* appears. The head movements are more resistant to anoxia than the limb movements, but the two types of early response are quite distinct from one another at this time. Stimulating one does not bring the other into play. They are, indeed, true reflexes.

1. They can be elicited only for brief intervals while metabolic activities are at their best. They disappear under anoxia. Myogenic responses do not.
2. The relaxation period is rapid; in myogenic responses it is sustained.
3. There is a definitely perceptible latent period during which a second stimulus fails to bring forth a response. Such latency is absent in myogenic responses.
4. The responses are stereotyped. They do not show the molding characteristics of myogenic responses when stimulus position is varied.

When micro-electrodes are used to stimulate the body surface over the cord, some distance caudal to the forelimb, the same primary outward and backward twitch of the limb occurs. This seems to be evidence of an upward conduction in the cord with at least one interneuron involved, for stimulating faradically elsewhere on the body surface at an equal distance from the limb yields no movement.

A study of pyridine-silver cord sections shows that all the nervous elements are now present for such reflex acts as these. As a matter of fact, they were present at the time of myogenic responses except for the fact that their intrinsic synaptic connections were as yet incomplete. There are sensory fibers whose peripheral ends pass to tissues immediately beneath the epithelium of the forelimb, and whose central branches constitute a dorsal root and dorsal funiculus. Motorneurons are assembled in two groups in the ventral gray. (See Figure 3). There is a medial group for trunk musculature and a lateral group for the limbs. Commissural and associational neurons are present—the former near the dorso-medial border and the latter near the ventrolateral border of the dorsal funiculus.

Commissural fibers course ventrally and cross the floor plate to ascend in a tract close to the motor neurons for the trunk. The associational group of neurons send their axons into the lateral funiculus passing close to the motor limb nuclei, and synapse with them in the reflex stage of development.

Thus up to the time of the appearance of the limb reflex, there is no close relationship between primary sensory neurons and secondary neurons. A few collaterals from the dorsal funiculus do pass a short distance toward the associational group of cells, but few reach them. But

in the motile reflex stage these connections are finally made, and some larger collaterals even reach motor neurons directly to effect a typical two-neuron, stretch-afferent, reflex arc. The largest new collaterals first grow in the brachial region, and correspond exactly with the first reflex response that we observed appearing in the upper limb. Commissural fibers as yet effect no connections with the trunk nuclei.

Such evidence as we have discovered by correlated histologic and physiologic experiment leads us to believe that these early forelimb movements are local, unisegmental, homolateral, two-to-three neuron, reflex arcs. Mammalian behavior has its genesis not in a mass reaction or total pattern of response like that of lower vertebrates, but in these relatively simple reflexes which are at first entirely non-integrated.

As development proceeds, many new reflexes make their appearance. Progressively the following independent reflexes were observed:

1. Local elbow flexion at 16 mm.
2. Local wrist flexion at 17 mm.
3. Movements in proximal parts of hind limb at 15-16 mm.
4. Movements of the knee joint and tail at 17.5 mm.
5. At first, the head can be stimulated only at the snout (13-14 mm.). But in 15-16 mm. specimens contra-lateral flexion is obtained from all parts of the face except those regions supplied by the ophthalmic division of the 5th nerve. Here a flexion response to the same side occurs. With further development more and more parts of the face yield a homolateral response until only the ear region yields contralateral flexion.

Though they are at first isolated, these local responses are gradually brought together in more generalized patterns by the longitudinal tracts which can be seen developing in the cord and later make connections with the afferent and efferent nuclei involved.

The earliest longitudinal (secondary) pathway, primarily ascending, is a ventral one formed by the axons of the commissural group of neurons. Impulses carried in this pathway first gradually effect connections with head and neck nuclei. These commissural neurons, lying as they do, close to the dorsomedial border of the dorsal funiculus, later receive sensory fibers from this funiculus. Hence, by the 17 mm. stage, forelimb movement initiates neck contraction as well. Later hindlimb responses call forth both forelimb and head responses. Soon too, collaterals from this ascending ventral column run to the motor neurons for trunk musculature, so that head and trunk responses become associated.

Fibers growing caudally from the midbrain and medulla, on the contrary, never reach any given cord level until ascending fibers from that level have already reached the medulla. Again, most of these descending fibers travel in the ventral funiculus where they synapse with motor neurons for the trunk muscles more effectively than with those for the limbs. Consequently limb responses tend to be less well integrated with trunk responses than are the head responses of the early embryo.

If, now, the placenta is detached from the uterine wall, or if the maternal animal with placenta intact is allowed to breathe atmospheres low in oxygen content, the local reflex responses soon become depressed. At first, just as in the adult organism, partial anoxemia has an exhilarating effect, enhancing local responses so that they are even more brisk and more easily elicited than normally. But soon they become sluggish and disappear entirely. Meanwhile, head and trunk movements become exaggerated, more sustained and more tonic. Thus, during anoxia the quality of behavior closely resembles the mass reactions described in Amblystoma and those described in the rat and man by Angulo and Hooker. Indeed, in the initial stages of oxygen want all motor neurons capable of function are marshalled in massive discharge—just as happens in any form of asphyxiation even in the fully developed adult.

Such gross activity extends even to smooth muscle and respiratory-like responses. In the well oxygenated fetus initial gut movements first appear as local segmental constrictions. At a later stage of development precisely integrated waves of peristalsis move over the stomach and intestine. But during anoxia the gut twists and coils in massive agonal writhing. Similarly the well oxygenated fetus *in utero* is entirely apneic. As early as the 30 mm. stage, however, the neural pathways for respiratory activity are laid down, and, though normally inactive, can be stimulated to activity by altering the blood-gas relationships between fetus and mother. Anoxia initiates respiratory-like movements of the thorax and abdomen. These are shallow and ineffectual at first, but very quickly attain a gasp-like quality. The fetus begins to aspirate amniotic fluid. In this instance, it can be stated categorically again that early mass motility is as abnormal as are these respiratory efforts *in amnio*. Both are signs of artificial anoxic distress when they are encountered in observations on young embryos. The mass activity during asphyxia is what investigators see when they examine early embryos removed from the uterus. It is this activity that has led to the erroneous belief that behavior in man has its genesis in a "total pattern" like that of the larval amphibian studied so extensively by Coghill.

Let us grant that the Gestalt psychologist is correct in advocating a consideration of the total organism against a background of its total environment. When we do so in the case of the mammal we do not end up with the type of a genetic theory of behavioral development that has been advocated by the Gestalt school. Quite on the contrary, a rigid adherence to the rules of the game indicates that early behavior originates as discrete, non-integrated, precisely localized reflex responses.

Summary

1. Structural development permits somatic motor function to begin in the mammalian embryo when the organism is just assuming the morphologic features which characterize its species.

2. The time at which movements begin spontaneously *in utero* is unknown, but it is probably days or even weeks after the first simple movements can be elicited by stimulation.

3. The first movement that can be obtained in an embryo is related to some maturation of its skeletal muscle fibers. Myogenic responses appear a day to a week before movements can be elicited through functional reflex arcs.

4. A period of neuromotor response probably precedes reflex activity.

5. The first reflexes in mammals are of at least two types: (a) limb movements that occur in response to stretch or pressure; (b) head movements that result from light tactile stimulation of facial areas. The former are homolateral, the latter often contralateral. The difference between these two types of responses is clearly explained by the structural differences in the parts of the nervous system involved. A close correlation exists between the time of appearance of these reflexes and the time of development and completion of 2-3 neuron reflex arcs in the central nervous system.

6. Impairment of respiratory conditions in the embryo has a profound effect on these early reflexes. In the first moments of a declining oxygen supply, elicitation of reflexes may be enhanced. As asphyxia progresses, reflexes are abolished or change their character, e.g., homolateral head movement may become contralateral or vice versa. Rhythmicity of movement occurs under duress. During asphyxiation all motility is finally depressed, but for some time before this occurs all motor units capable of functioning can be induced to discharge or do so spontaneously. The quality of behavior under anoxic distress alone can be characterized as "mass activity". It is not at all like the precisely localized reflex responses that occur under good physiologic conditions in the normal course of development.

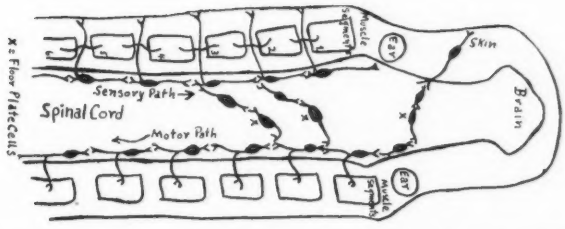

FIGURE 1. Diagram of the sensory-motor mechanism of a salamander embryo which accounts for a cephalo-caudal progression of movement away from the side stimulated. Arrows indicate direction of conduction.

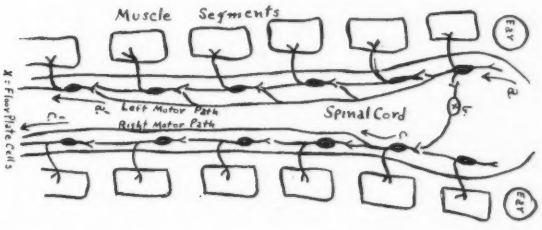

FIGURE 2. Diagram of the neuromotor mechanism of a salamander embryo which allows an initial impulse (a, a') to be followed by a contralateral secondary impulse (c c') through a connector neuron (b). In this way massive flexures of the trunk becomes possible.

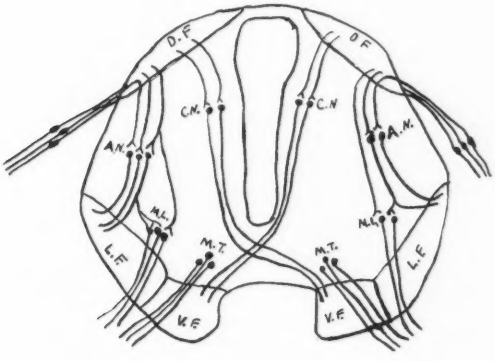

FIGURE 3. Diagram of the cross section of the cord in a mammalian embryo at the time of initial reflex activity. The earliest connections of the sensory neurons at the lateral end of the dorsal funiculus (D.F.) are with associational neurons (A.N.) to effect unisegmental reflex arcs with primary motor neurons of limb muscles (M.L.) Some of these afferents effect direct connections. There are as yet no collaterals from the commisural neurons (C.N.) to primary neurons of the trunk (M.T.). L.F.—lateral funiculus. V.F.—ventral funiculus.

BOOK REVIEWS

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. Newman Dorland, M.D. 22nd edition. Leatherette. 1736 pages with 720 illustrations. Philadelphia and London: W. B. Saunders Company, 1951. $10.00.

The new edition of the "Dorland" dictionary features many changes. In addition to the new words there is included a section on medical etymology, and an extensive chart on drug therapy. The dictionary deals with terms in the fields of Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, and Medical Biography. New charts and plates have been added. The print and form of the pages have been altered. The 22nd editions also measures slightly larger than previous editions. The dictionary remains a standard in its field, and in its broad range of usefulness.

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A TEXTBOOK OF MEDICINE. Edited by Russell L. Cecil, M.D., and Robert F. Loeb, M.D. Cloth. Eighth edition. 1627 pages with 204 figures. Philadelphia and London: W. B. Saunders Company, 1951. $12.00.

The new edition of "Cecil." written in collaboration with Dr. Loeb and a staff of 166 contributors, re-establishes this text as a standard in the field. The form of the book has been changed, thus necessitating a complete resetting of the type. The authors have stressed the physiologic, biochemical and psychologic aspects of disease under each of the headings and particularly in the introductory sections of each of the disease groups. Diseases of collagen have been put under one heading with an excellent introductory. Many new diseases are discussed, such as rickettsialpox and Q fever. Discussion on therapy are brought up to date, including those on the newer antibiotics. As before, this continues to be a leading text in internal medicine.

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THE PATHOLOGY OF INTERNAL DISEASES. By William Boyd, M.D. Cloth. Fifth edition. 866 pages with 391 illustrations and 11 plates. Philadelphia: Lea and Febiger, 1950. $11.00.

The new edition of this work contains many new discussions as well as a number of rewritten chapters. With the extensive revisions, the author has included the newer concepts of disease in logical and clear presentation. There is a section of the relation of symptoms to lesions following each major pathologic discussion. Dr. Boyd had an interesting, readable and often humorous style. Diseases covered are those which are ordinarily found on the wards of a teaching hospital on the medical service. The book is well illustrated. It is highly recommended to all students and practitioners.

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CURRENT THERAPY 1951. Edited by Howard F. Conn, M.D. Cloth. 699 pages. Philadelphia and London: W. B. Saunders Company, 1951. $10.00.

This volume cites the approved methods of treatment as of the present time. With the rapidity of progress in medical therapeutics in recent years, a volume of this type fills a definite need. The discussions in this book are succinct and exact. Diagnosis is discussed where the author considers it to be an integral part of therapy. As stated by Dr. Conn, "Sound therapy must be balanced therapy based on an accurate diagnosis and the use of effective therapeutic agents." Where therapeutic methods not fully tested are cited, they are so designated. The book is comprehensive and authorative. Dr. Conn, his 12 consultants and 275 contributors have presented a valuable reference work to the medical profession.

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THE NORMAL ENCEPHALOGRAM. By Leo M. Davidoff. M.D., and Cornelius G. Dyke, M.D. Cloth. Third edition. 240 pages with 190 illuctrations. Philadelphia: Lea and Febiger, 1951. $6.00.

This is an outstanding book dealing with encephalography. It incorporates a discussion of general considerations including techniques, indications and effects of the procedure. Detailed discussion of the anatomy and the radiologic findings follows. The book includes complete and extensive illustrations of air studies. Correlated with its companion volume, **The Abnormal Pneumoencephalogram**, the book is of great value to radiologists, neurologists, neurosurgeons, and anatomists.

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THE ABNORMAL PNEUMOENCEPHALOGRAM. By Leo M. Davidoff, M.D., and Bernard S. Epstein, M.D. Cloth. 506 pages with 695 illustrations. Philadelphia: Lea and Febiger, 1950. $15.00.

This book admirably illustrates the role of the air-study roentgenogram in the diagnosis and localization of structural abnormalities of the brain. In addition to purely radiologic considerations, the authors present clinical material from their own and others' experience in the form of case studies, direct and differential diagnosis, statistical analyses, and reviews of the literature. The book is divided into two parts dealing with tumors, neoplastic and non-neoplastic, and with non-tumorous lesions of the central nervous system including congenital, degenerative and infectious conditions. The illustrations are superb, showing plain roentgenograms, pneumoencephalograms, surgical and pathologic specimens. The book is highly recommended to the radiologist, the neurologist, the neurosurgeon, and the neuropathologist for both study and reference.

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HANDBOOK OF PEDIATRIC MEDICAL EMERGENCIES. By Adolph G. DeSanctis, M.D., and Charles Varga, M.D. Cloth. 284 pages with 51 illustrations. St. Louis: The C. V. Mosby Company, 1951. $5.00.

Written by 13 contributors, this book is intended as a guide in the management of those conditions in pediatrics which call for rapid, emergency therapy, including early diagnosis leading to therapy. There is also included a section on pediatric procedures commonly employed. The organization is according to systems. The book is written in simple outline form with many tables. It will be found useful as a reference manual to pediatricians, residents, and general practitioners.

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CORONARY CIRCULATION IN HEALTH AND DISEASE. By Donald E. Gregg, M.D. Cloth. 227 pages with 73 illustrations. Philadelphia: Lea and Febiger, 1950. $4.50.

The rising incidence of coronary disease at the present time makes this a particularly vital and timely volume. Coronary circulation is discussed from the points of view of morphology, experimental and pathological study. The author attempts to present the present status of our knowledge concerning the coronary circulation, with all its characteristics and peculiarities. The book is recommended to internists, cardiologists, and physiologists.

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PRINCIPLES OF INTERNAL MEDICINE. By T. R. Harrison, editor-in-chief. 1,590 pages with 245 illustrations. Cloth. Philadelphia and Toronto: The Blakiston Company, 1950. $12.00.

This new textbook of medicine presents a concept of mechanisms and pathophysiology of disease. This serves to correlate the pre-clinical studies with those of clinical medicine. Not only is the first part of the book devoted to the physiology of symptoms, but, heading each section there is a discourse on the general considerations of the group of disorders to be discussed. The general plan of the book, as well as that of certain of the diseases, is unconventional, but more interesting, for that reason. The understanding of the more common disorders is stressed, with condensation of the discussion of the rarer conditions. The Board of 5 editors and 48 contributors have presented an original and courageous volume that is highly recommended to all students and practitioners of medicine.

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COMMUNICABLE DISEASES. Edited by Roscoe L. Pullen, M.D. Cloth. 1,035 pages with 253 figures and 20 color plates. Philadelphia: Lea and Febiger, 1950. $20.00.

Written by collaboration of 53 contributors, principally from the staff of the Charity Hospital of

Louisiana at New Orleans, this work is a compendium of the present status of clinical knowledge concerning communicable diseases. With the profound changes in prognosis and management of these diseases, following the wide use of the newer therapeutic agents, this book becomes particularly timely. Following a clinical orientation, Dr. Pullen has organized the book according to symptomatology, rather than etiology, in order to stress diagnosis. Thus, the diseases are classified as those with predominant skin manisfestations, predominant respiratory, eye, central nervous system, widespread systematic, and enteric manisfestations. There is a section on parasitic diseases. A special section is included, entitled: "Communicable Diseases Capable of Becoming a Potential Menace." A helpful section on pediatric procedures is added. The illustrations are excellent. Practitioners and students will find this book excellent for study in diagnosis and treatment of the communicable diseases.

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THE NEUROSES. By Walter C. Alvarez, M.D. Cloth. 667 pages. Philadelphia and London: W. B. Saunders Company, 1951. $10.00.

Dr. Alvarez, an internist, has become well-known recently for his psychosomatic approach to medical problems. This thesis is that all physicians must be, to a certain extent, psychiatrists. The emotional disorders of the majority of patients are presented or become evident to the practitioner. in particular the differentation of physical from functional disease. The neuroses are described as they are met by the surgeon, the gynecologist, the urologist, etc. Written for the non-psychologist, the book succeeds in presenting the neuroses and the minor psychoses in a clear and interesting fashion.

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HEART DISEASE. By Emanuel Goldberger, M.D. Cloth. 651 pages with 229 illustrations on 90 figures. Philadelphia: Lea and Febiger, 1951. $10.00.

The author of this new book stresses the use of ordinary methods of physical examination in diagnosis of heart disease. He writes for the general practitioner who has at his disposal his powers of observation, the use of his senses, and the commonly employed procedures of fluoroscopy and electrocardiography. The newer methods are presented as adjuncts to physical diagnosis. Included here are electrokymography, angiocardiography, ballistocardiography, catheterization study, etc. The book is divided into five sections: the normal heart, the abnormal heart cardiac syndromes, cardiac abnormalities (etiologic), and conditions complicating heart disease. The book is well written, succinct and complete. It will be found of value to all practitioners and students.

RENAL DISEASES. By E. T. Bell, M.D. Cloth. Second edition. 448 pages with 123 illustrations. Philadelphia: Lea and Febiger, 1950. $8.00.

This book is a discourse on the pathologic and clinical manifestations of kidney disease. The second edition draws from the additional information of 18,000 added autopsies, together with the added knowledge of recent investigation. The chapters on tubular disease and extra-renal azotemia have been enlarged. Other chapters include those on anomalies, hydronephrosis, glomerulonephritis, pyelonephritis, diseases of the blood vessels, metabolic disorders, and tumors of the kidneys. Pathologists and clinicians will find this an excellent treatise on renal disease.

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PATTERNS OF DISEASE. By Frank L. Apperly, M.D. Cloth. 456 pages with 50 figures and 37 charts. Philadelphia, London, Montreal: J. B. Lippincott Company, 1951. $8.00.

The author as a professor of pathology has written this book from the point of view of physiologic pathology. He stresses the presentation of disease process as altered function before there is altered structure. He takes cognizance of the compensatory mechanisms of the body as necessary for the complete understanding of symptomatology. The discussions are brief and clear, the book being well outlined charted. Illustrations are for the most part diagrammatic drawings. This book will be found useful as an adjunct to the textbooks of pathology.

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EPITOME OF THE U.S.P. AND N.F. Ninth edition. Cloth. 255 pages. Philadelphia, London, Montreal: J. B. Lippincott Company, 1951. $2.50.

This little book, by the Council on Pharmacy and Chemistry of the American Medical Association, contains the official titles. synonyms, brief definitions. concise descriptions of the physical properties, dosage, actions and uses of the most useful drugs listed in the United States Pharmacopoeia and the National Formulary.

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THE BASES OF HUMAN BEHAVIOR. By Leon J. Saul. M.D. Cloth. 150 pages. Philadelphia, London, Montreal: J. B. Lippincott Company, 1951. $4.00.

Subtitled, "A Biologic Approach to Psychiatry," this book is intended as a textbook in psychiatry for first year medical students. A concept of physiologic and psychologic interaction is well presented. The book gives the student a firm basis for the understanding of psychodynamics, and the role of psychologic factors in disease. It is recommended to all students and physicians.

BACTERIAL WARFARE

(Cont'd from page 144)

Of the public health measures, vaccination may be considered. However, vaccinating everyone against all possible B.W. agents would be an impossible task. Then, the B.W. use of microorganisms of sufficiently different antigenic makeup or strain would nullify the value of mass vaccination.

Other subjects are important, but space does not permit a discusion of detection and identification of B.W. agents after their use; epidemiological intelligence; a more detailed analysis of public health control of these infections; psychological use of B.W. to cause panic; the use of B.W. agents against livestock e.g. rinderpest, foot-and-mouth disease, fowlpox, etc.). Many of these phases are covered in the C.D.A. manual, "Health Services and Special Weapons Defense."

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SCHOOL NOTES AND NEWS

FACULTY NEWS

It is with great pride that we take this opportunity to welcome Dr. F. Joseph Mullin as Dean and Professor of Physiology at The Chicago Medical School. Dr. Mullin brings with him a wealth of knowledge and experience both in Physiology and in medical education and administration.

Born in El Paso, Texas, in 1906, Dr. Mullin received his Bachelor of Arts degree from the University of Missouri in 1929 with Honors in Psychology. He then went to the University of Chicago where he received his Master of Science degree in 1932 and was awarded his Doctor of Philosophy degree in Physiology in 1936. Dr. Mullin then returned to Texas as Assistant Professor of Physiology at the University of Texas in Galveston where he remained until 1938 when he once more returned to the University of Chicago as Instructor in Physiology in the College.

He served in the Department of Physiology and rose from Instructor to Assistant Professor to Associate Professor. In 1944, Dr. Mullin was appointed to the position of Dean of Students, Division of Biological Sciences, which included the Medical School. In 1946, Dr. Mullin won the award for excellence in teaching. The next year, he was appointed Secretary of the Faculties of the University of Chicago. He held both the above positions in addition to being Associate Professor of Physiology until he resigned these positions to come to The Chicago Medical School as Dean and Professor of Physiology in March, 1951.

Dr. Mullin has been active in community and church groups and is a member of the American Physiological Society, Society of Experimental Biology and Medicine, Sigma Xi and is also a member of the Chicago Literary Club. In addition to the above societies, Dr. Mullin is a member of the Committee of Student and Personnel Practices of the Association of American Medical Colleges and also of the Committee on Internes and Residents. He is also Chairman of the National Inter-Association Committee on Interneships. He has published numerous articles in the fields of pain sensitivity, blood circulation, physiology of sleep and medical education.

We take great pleasure in welcoming Dr. Mullin to The Chicago Medical School and trust that his association with us will be a long and mutually beneficial one.

We would like to take this opportunity to announce the appointment of Dr. Andrew Howard Ryan as Dean of Students at The Chicago Medical School.

Dr. Ryan received his Doctor of Medicine degree from Washington University in St. Louis in 1910. He was Instructor in Physiology and Pharmacology at the University of Pittsburgh, and held the chair of Physiology at the University of Alabama, Tufts Medical School and the University of Maryland. He was Lecturer in Applied Physiology at Yale University, where he was the originator of that subject. Dr. Ryan was also an Associate Physician with the United States Public Health Service. In 1944 Dr. Ryan was appointed Associate Professor of Physiology and Pharmacology at The Chicago Medical School.

Dr. Ryan has carried out research in

many fields including asphyxia and resucitation, goiter, actions of magnesium sulfate, caffeine, strychnine, cinchophen, autonomic drugs, and the question of industrial fatigue and efficiency.

Besides being a member of Alpha Omega Alpha and Nu Sigma Nu, Dr. Ryan is a member of the American Physiological Society, the Society of Pharmacology and Experimental Therapeutics, the American Statistical Association, the Biometric Society, the National Institute for Industrial Psychology in Great Britain, and the American Medical Association.

As Dean of Students, Dr. Ryan will be in charge of the Admissions Committee, of Student Affairs and Activities and of Student Health.

We are happy to announce the promotion of a man of Dr. Ryan's ability to the position of Dean of Students of The Chicago Medical School.

It is with pleasure that we announce the appointment of Miss Edna A. Luebeck as Assistant to the Dean of The Chicago Medical School. Miss Luebeck, who served as Administrative Assistant for the past twenty-five years is well known and loved by all of us who have had the opportunity to come in contact with her. Through the years of trial and difficulty that preceded accreditation of The Chicago Medical School, she remained loyal and devoted to the best interests of the

institution. Her part in the continued progress of the School, has been considerable. Her present promotion to Assistant to the Dean comes as a well deserved tribute to her activities in behalf of the school.

Dr. Israel Davidsohn has been elected member of the Academy of Forensic Sciences and Chairman of the Blood Bank Committee of the Illinois Society of Pathologists.

Dr. Paul Egel has been elected a Fellow of the International College of Surgeons.

Dr. Harold Elishewitz has been appointed to the Editorial Board of the Medical Entomology Section of the Laboratory Digest.

Dr. Samuel J. Turner has been elected Fellow of the Chicago Gynecological Society, and of the American College of Surgeons, and has been appointed attending obstetrician and gynecologist, Mount Sinai Hospital in Chicago.

ALUMNI NEWS

The Faculty and Alumni Association extend their heartfelt sympathy to the family and friends of Dr. Hyman Yanofsky, Class of 1920, who passed away November 30, 1950.

Class of 1950

Dr. Irwin S. Morse, former Editor of the QUARTERLY, has been appointed a resident in Surgery at the Coral Gables Veterans Administration Hospital. Dr. and Mrs. Morse are expecting their second child later this year.

Drs. Philip Oransky and Abraham Ludwig have been appointed residents in Medicine at the Coral Gables Veterans Administration Hospital.

Dr. Melvin Ehrich has been appointed a resident in Pediatrics at the Charity Hospital, New Orleans, Louisiana.

Dr. William Anderson has been commissioned in the United States Army Medical Corps.

Dr. Murray W. Brown has been appointed to a General Practice residency at the Lafayette General Hospital, Lafayette, Louisiana.

Dr. David Safadi has accepted a residency in Pathology at Kings County Hospital, Brooklyn, New York.

Dr. Jerome Z. Litt has been appointed resident in Dermatology at Kings County Hospital.

Dr. Herbert Fishbein has been appointed Resident in Radiology at Maimonides Hospital, Israel Zion Division, Brooklyn, New York.

Class of 1949

Congratulations to Dr. and Mrs. Sidney Kase of Antioch, California on the birth of a daughter, Sheryl Lee, on May 2, 1951. Dr. Kase also announces the opening of his office for General Practice and Surgery in Antioch.

Congratulations are in order to Dr. and Mrs. Hulbert J. Kanter on the birth of triplets, Kevin Lance, Kate Leslie and Kyle Linda on May 8, 1951.

Class of 1948

Dr. Theodore Cohen has been appointed Assistant Resident in Internal Medicine in the New York University Division of Bellevue Hospital, New York City.

Class of 1947

Dr. Myron Saline is now serving in the Armed Forces Medical Corps, after having left the service of the Queens General Tri-Boro Hospital.

Congratulations to Dr. R. R. Simner on his marriage to the former Miss Barbara Ann Ringel of New York City on April 1, 1951.

Dr. Louis J. Polskin of Lakeland, Florida has been commissioned a Captain in the Army Medical Corps.

Class of 1942

Congratulations to Dr. Samuel Stymacin on his marriage to Ida H. Selick in Brooklyn, New York, Dec. 24, 1950.

Class of 1940

Dr. Warren W. Greene of Pacific Palisades, California, has been certified by the American Board of Anaesthesiology.

Class of 1936

Dr. Louis H. Turek has been appointed Clinical Assistant in the Department of Medicine of The Chicago Medical School.

Dr. Stanley B. Abelson has resigned from the faculty of The Chicago Medical School and has now taken up residence at 208 North Church St., Carmi, Illinois.

STUDENTS NEWS

Class of 1951

Graduation exercises of the Class of 1951 of The Chicago Medical School were held in the John B. Murphy Auditorium of the American College of Surgeons on June 23, 1951. President John J. Sheinin conferred degrees of Bachelor of Medicine on the 63 candidates who were presented by the Dean, Dr. F. Joseph Mullin. The speaker was the Right Reverend Dudley Scott Stark, Bishop of the Episcopal Diocese of Rochester, New York and a member of the Board of Trustees of The Chicago Medical School.

The Editorial Board and the Staff of the QUARTERLY join the Administration, the Faculty, and the student body of The Chicago Medical School in extending their heartiest congratulations to the Class of 1951 on the occasion of their graduation. The road has been long and the work hard, but we now wish them good fortune and the realization of the fruits of their labor. We know that they will be a credit to the school in their internship year, and in the career that lies ahead of them. When they took their diplomas on June 23,

1951, they took the best wishes of all of us with whom they have been associated during the past four years.

Congratulations are in order to Melvin M. Pick on his being awarded Honorable Mention in the competition for the Schering award for 1950 on "The Clinical Uses of Steroid Hormones in Cancer."

The QUARTERLY congratulates its Medical Editor, Arthur Bresler, and his wife Ruth Bresler on the birth of their second child, Mark Steven on June 7, 1951.

Best wishes to the following graduating seniors on their marriages:

Dave Parker to Miss Helen Cooperstein, of the nursing staff of Mount Sinai Hospital, in May of 1951.

Sam Schiff to Miss Jean Brody of Chicago, on November 23, 1950.

Al Schwartz to Miss Gloria Bell on June 17, 1951.

Adolph Boltax to Miss Kay Mutchnick, of the staff at Mount Sinai Hospital, on June 24, 1951.

Morton Doblin to Miss Arline Perlman of Chicago on June 24, 1951.

Al Kraft to Miss Selma Warshaw on June 24, 1951.

Congratulations to Frank Friedman on his engagement to Miss Eunice Caeser of Chicago in April 1951.

Congratulations to the Sam Farbers on the birth of their second son, Michael Bruce, on March 28, 1950.

Best wishes to Bert and Caryl Carnow on the birth of a son, David Robert, on February 27, 1951.

Class of 1952

Best wishes to Marvin Markowitz and the former Miss Beatrice Brody, both of Brooklyn, New York, on the occasion of their marriage June 24, 1951.

Class of 1953

Best wishes to Edward Diamond on his marriage to the former Miss Joan Chase of Newark, on June 14, 1951.

Congratulations to Robert J. Langs of New York and the former Miss Joan Schwartz of Pittsburgh, Pa., on the occasion of their marriage on July 5, 1951.

Class of 1954

Congratulations to Walter Jacobs and the former Miss Dorothy Joan Kaplan of Brooklyn, New York on the occasion of their marriage June 23, 1951.

Best wishes are also in order to Sheldon L. Schein and the former Miss Lila Stumacher of Brooklyn, New York on the occasion of their marriage June 19, 1951.

Congratulations to Miriam and Herbert Snyder on the birth of a son, Robert Geoffrey, on March 8, 1951.

ORGANIZATION NEWS

Student Council

The Student Council, in its constant attempt to represent the student's point of view made what represented an unsuccessful attempt to supply used books to the students. However, the plan has not been abandoned and next fall when there will be a great necessity for these books at a reduced price, we will re-test the operation.

In the campaign to enact Bill No. 490, the Student Council planned, with the assistance and guidance of the Physiology Department, a mass meeting of the entire student body. At this meeting they were told of the importance of the legislation and how we, as students, could aid in its passage. Many students wrote letters asking their respective Congressmen to support the bill. We would like to thank those students who wholeheartedly supported this drive which directly concerns each and every one of us.

Again, we would like to ask all organizations to submit calendars for the coming quarter.

We would like to express our gratitude to Dean Ryan since he has expressed his desire to see the Council expand and for his willingness to be a sincere arbitrator in student affairs.

Phi Delta Epsilon

Phi Delta Epsilon members, old and new, with their guests, made merry at the Yacht Club (the floating entertainment spot of Chicago) on Saturday, May 19. It was all in the honor of their graduating Seniors. Among the honored group, the Chapter has chosen Chuck

Fadem as its entry to the Annual Cover Award contest. Sherm Goldberg will mold his merits into a winner, we hope.

The proposed series of educational lectures began as scheduled on Friday, May 11. Dr. Gaberman treated his topic, "The History of Medicine," in a novel way. He drew forth anecdotes from his war experience, which served the purpose of entertainment as well as being a very vital and fascinating way of disclosing an era of medical history.

The "Choosing a Specialty" lecture series will continue with Professor Giles speaking on "Surgical History," followed by Dr. Eisenberg with a talk on Internship Orientation; and then lectures on General Practice, Internal Medicine, Surgery, Obstetrics and Gynecology, Pediatrics, Psychiatry, Eye, Ear, Nose and Throat, Urology, and Orthopedics. Some of the questions to be considered will be: why and why not choose a particular field; the type of work, and the type of patients encountered; the limitations of the field; residency, where and how long; general practice before specialty; getting hospital connections; the type of community to look for; and the problems in setting up practice.

New officers for the coming year are:

President .....George E. Ehrlich
Vice President .....Robert Langs
Secretary .....Jack Handel
Treasurer .....Walter Griesbach
Marshal .....Peter Griesbach
Senior Senator .....David Schulman

Phi Lambda Kappa

The new officers for the coming year have been elected by the Alpha Rho Chapter, Phi Lambda Kappa and they are:

President .....Sanford I. Cohen
Vice President .....Kenneth Cohen
Secretary .....Harold Fischer
Treasurer .....Stuart Cohn
Corr. Secretary....Eugene Trachtenberg
Alumni Scribe .....Norman Blass

It is with much regret that we see two of our officers leave this year and many thanks must be extended to Art Lisbin, our graduating president, and to Mel Pick for his two outstanding years as treasurer. We also bade all our senior fraters a fond farewell by means of our annual senior dinner dance which was held May 26th at the Furniture Club. This dance was again held in conjunction with Alpha Alpha Chapter of the University of Illinois.

Plans for next year are in the formulative stage but we hope to again equal or even surpass the number of activities that took place this year. We are especially pleased that we again won this year the annual best chapter award given out by our national directorate. This is the second year in a row that we have won this trophy and if we win it once more we can have it for permanent possession.

SPLEEN

(Cont'd from page 126)

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THE BLAKISTON COMPANY

Harrison, T. R. ..... "Principles of Internal Medicine"

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Kampmeier, Rudolph H. ..... "Physical Examination in Health and Disease"

LEA AND FEBIGER

Bell, E. T. ..... "Renal Diseases"
Boyd, William ..... "The Pathology of Internal Diseases"
Davidoff, Leo M. and Dyke, Cornelius G. ..... "The Normal Encephalogram"
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Goldberger, Emanuel ..... "Heart Disease"
Gregg, Donald E. ..... "Coronary Circulation in Health and Disease"
Pullen, Roscoe L. ..... "Communicable Diseases"

J. B. LIPPINCOTT COMPANY

Apperly, Frank L. ..... "Patterns of Disease"
Berens, Conrad and Siegel, Edward ..... "Encyclopedia of the Eye"
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Reich, Walter and Nechtow, Mitchell J. ..... "Practical Gynecology"
Saul, Leon J. ..... "The Bases of Human Behavior"
Zieman, Stephen A. ..... "World Surgery 1950"

MACMILLAN COMPANY

Green, David E. and Knox, W. Eugene ..... "Research in Medical Science"

C. V. MOSBY CO.

Adler, Francis Heed ..... "Physiology of the Eye"
Berman, Jacob K. ..... "Principles and Practice of Surgery"
Cleckley, Hervey ..... "The Mask of Sanity"
DeSanctis, Adolph G. and Varga, Charles ..... "Handbook of Pediatric Medical Emergencies"
Duke-Elder, Sir Stewart ..... "The Practice of Refraction"
Herrman, George R. ..... "Methods in Medicine"
Kuhn, Hedwig S. ..... "Eyes and Industry"
Titus, Paul ..... "The Management of Obstetric Difficulties"

W. B. SAUNDERS CO.

Alvarez, Walter C. ..... "The Neuroses"
Anson, Barry J. ..... "An Atlas of Human Anatomy"
Cecil, Russell L. and Loeb, Robert F. ..... "A Textbook of Medicine"
Colonna, Paul C. ..... "Regional Orthopedic Surgery"
Conn, Howard F. ..... "Current Therapy, 1951"
Curtis, Arthur Hale and Huffman, John Wilke ..... "Textbook of Gynecology"
Dorland, W. A. Newman ..... "The American Illustrated Medical Dictionary"
Harrow, Benjamin ..... "A Textbook of Biochemistry"
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Pullen, Roscoe L. ..... "Medical Diagnosis"
Smith, Ferris ..... "Plastic and Reconstructive Surgery"
Sodeman, William A. ..... "Pathologic Physiology"
Sweet, Richard H. Illustrations by Arroyo, Jorge Rodriguez ..... "Thoracic Surgery"
Wilder, Russel M. ..... "A Primer for Diabetic Patients"

CHARLES C. THOMAS

Engle, Earl T. ..... "Menstruation and Its Disorders"

THE WILLIAMS AND WILKINS COMPANY

Mock, Harry E. ..... "Skull Fractures and Brain Injuries"